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OF
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Report of a Study
Part 2

FOOD SAFETY POLICY

Scientific and Societal Considerations

March 1979

National Academy of Sciences
Washington, D.C.

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FOOD SAFETY POLICY:
SCIENTIFIC AND SOCIETAL CONSIDERATIONS

Part 2 of a Two-Part Study of the
COMMITTEE FOR A STUDY ON SACCHARIN AND FOOD SAFETY POLICY

A Report Prepared in Response to Public Law 95-203
(Saccharin Study and Labeling Act)

Committee for a Study on Saccharin and Food Safety Policy

Institute of Medicine and the National Research Council/
Assembly of Life Sciences
National Academy of Sciences
Washington, D.C.

March 1, 1979

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NOTICE

The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the Councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

The work on which this report is based was performed pursuant to Contract No. 223-78-2145 with the Food and Drug Administration.

NATIONAL ACADEMY OF SCIENCES

OFFICE OF THE PRESIDENT
2101 CONSTITUTION AVENUE
WASHINGTON, D.C. 20418

February 28, 1979

The Honorable Joseph A. Califano, Jr.
Secretary of Health, Education,
and Welfare
Washington, D. C.

My dear Mr. Secretary:

This will transmit "Food Safety Policy: Scientific and Societal Considerations," Part II of a report. Part I, "Saccharin: Technical Assessment of Risks and Benefits" was transmitted on 6 November 1978. This report was prepared by the Committee on Saccharin and Food Safety Policy, a joint committee of the Institute of Medicine and of the Assembly of Life Sciences of the National Research Council, under the terms of our Contract 223-78-2145 as required by Public Law 95-203.

Part I reported that saccharin is a carcinogen, viz., at sufficiently high dietary doses, over a lifetime, a considerable incidence of bladder tumors was elicited in male rats born to mothers who had also received the same level of saccharin since their own weaning. Evidence was also reported indicating that saccharin is a 'promoter,' i.e., high concentrations of saccharin that do not, in themselves, occasion a neoplastic transformation in several test systems, do occasion such a response when the same systems are exposed to known carcinogens at concentrations below those at which the latter are otherwise effective. Lacking a meaningful dose response curve, lacking a sure calculus for extrapolating from rats to humans, and lacking reliable epidemiological evidence in man, Part I could not derive, with confidence, an estimate of the quantitative magnitude of the risk posed by saccharin under the circumstances of use in man. To use the apt phrase found in one of the letters in the appendix to Part II, Part I, in effect, concluded that "there is risk of a risk." However, the level of concern so generated is heightened by knowledge of the extensive consumption of saccharin in soft drinks by young children, by adolescents, and by women of child-bearing age.

Part II accepts these findings and takes them as a point of departure. After reviewing diverse aspects of food safety, risk assessment, benefit assessment, prevailing and alternative policies and strategies, Part II recommends: (a) that there be a single policy applicable to all foodstuffs, food additives and food contaminants and that the public official responsible for implementation of that policy be given sufficient flexibility to factor risks, benefits and other considerations into account when making a decision concerning a material that has been called into question, (b) that there be available to that official options other than decisions simply to ban or not ban, and (c) that to facilitate such implementation, materials under consideration first be categorized as exhibiting low, moderate or high risk.

The authors of the report are aware that they have offered a philosophy to underlie the institutional arrangements and procedures required, rather than a detailed blueprint. Their report, knowingly, does not address how matters come to attention, the express legal underpinning of the responsible agency, the authority of that agency, appeals mechanisms or other aspects of the formal procedures required if their philosophy is to become useful and effective.

The treatment of saccharin in Part II, within this proposed framework, then reveals the central difficulties before the committee, the government and the public. This report leaves to the government the task of defining more precisely the criteria for the three categories noted above. This omission, at least in some part, stems from disagreement within the committee concerning appropriate treatment of the combinations of the two principal variables: probability of occurrence and seriousness of the health effect in question. Patently, most thinking persons will dismiss, as a problem not requiring regulatory intervention, a low probability of a minor, reversible adverse health effect. And most will surely seek to remove from the food supply any substance which, under the circumstances of use, offers a high probability of some very serious adverse health effect.

But the problems that challenge the regulatory system are those in which there is a very low probability of a serious adverse effect (saccharin?), or those in which data are only suggestive and no reliable estimate of probability can be

offered (saccharin?), and those for which probability is moderately high but the effect in question is not severe and is reversible.

The five signatories to the formal minority statement make evident the division in the committee presumably reflecting a division of unknown dimensions in the American public. As I interpret their statement, they hold that, regardless of other considerations, only a zero probability of cancer is acceptable; if that probability is greater than zero, the substance should be deemed of high risk and removed from the food supply. They state that a risk-free diet is a right and argue that the government should assure that right by appropriate regulatory measures, rather than minimize undesirable outcomes by educational means when probability is already very low. If I understand correctly, most of the thirty other members of the committee would have been comfortable with assigning saccharin to the moderate risk category and then leave the government free to select among a number of alternative policies. And, although most committee members "believe that a total immediate ban of saccharin would not be a sound regulatory step at the present time," it is this basic difference that led to the otherwise surprising statement that, "Under the general food safety policy and risk categories proposed in this report, saccharin could belong in either the moderate or high risk category, depending upon the discretion of FDA."

The difference of opinion which led to this ambivalent statement is not a differing interpretation of scientific fact or observation; it reflects, rather, seriously differing value systems. In some part, these differences in view were deliberately built into the structure of the committee as its members were appointed although the viewpoints, in these regards, of less than half the committee were already known to us.

Estimation of risk is a scientific matter, albeit not always readily feasible. Decision concerning the acceptability and management of a given risk is an intrinsically political question to be returned to the polity for determination. And it is for that reason that I am pleased that this report makes evident that the three dozen individuals who served on the overall committee and its two principal panels were a microcosm of the American public. The issues stand revealed; decision can be made only by the political process.

Finally, allow me to utilize this opportunity to make known our deep appreciation to the committee and panels for their diligence and devotion to this task, particularly to the committee chairman, Dr. Frederick C. Robbins, and the panel chairmen, Dr. Walter A. Rosenblith, Dr. Clifford Grobstein and Dr. Emmanuel Farber as well as to their talented and hardworking staffs, particularly Dr. Elena Nightingale and Dr. Robert G. Tardiff.

Sincerely yours,

P Handler

Philip Handler
President

Enclosure

FOREWORD

This report, Food Safety Policy: Scientific and Societal Considerations, is Part Two of the work done by the joint Institute of Medicine/Assembly of Life Sciences Committee for a Study on Saccharin and Food Safety Policy. Part One, Saccharin: Technical Assessment of Risks and Benefits, was transmitted on November 1, 1978.

The entire study was requested by the Congress in November 1977 in the Saccharin Study and Labeling Act (PL 95-203). This act not only requested an assessment of the health risks and benefits of saccharin but also a more general analysis of food safety policy. It is this latter request to which the present report is responsive.

Recognizing that there are many substances in food about which health and safety questions have arisen, the committee has constructed a framework for analysis of such problems. This is a difficult and ambitious task. The committee has achieved much in the time available. Its broadly-based composition permitted it to examine these complex issues from multiple perspectives, taking into account not only the scientific facts but also the many social interests and values at stake in issues of food safety.

The study elucidates the current science base for making policy with respect to food safety. This fund of knowledge is highly pertinent not only to regulatory decision making but also to public education in the service of health. At the same time, the committee makes clear the severe constraints on present knowledge, and points to ways in which the science base can be strengthened in years to come.

The study considers ways in which the best available scientific information can, at any given time, be brought to bear on regulatory decisions and made usefully available to the public. In so doing, the committee arrives at recommendations aimed toward a system that would be comprehensive, consistent, distinguish among risk levels in a way that would have practical consequences and foster a variety of regulatory and educational approaches. Such a system is intended to facilitate the responsible judgment of legislators and administrators in the fullest possible knowledge of scientific data and informed public preferences.

In these exceedingly complex and significant tasks, the interdisciplinary committee reached a remarkable degree of consensus. Yet some points could not be resolved in the time available, and the unresolved issues are clearly spelled out. Those who have conducted the study view this as one step in a continuing process by which scientific knowledge of food benefits and risks can become deeper and the links of this knowledge to reasonable policy-making made stronger. They are careful and restrained in their analysis, sensitive to the many scientific uncertainties and value conflicts embedded in these issues. The step they have taken on the road to a sound food safety policy deserves thorough consideration by the American people.

David A. Hamburg, M.D.
President
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CONTENTS

FOREWORD David A. Hamburg, M.D. iii

COMMITTEE CHAIRMAN'S PREFACE xiii

PANEL CHAIRMEN'S PREFACE xvi

SCOPE AND ORGANIZATION OF REPORT xix

SUMMARY S-1

Chapter 1 FOOD AND HEALTH IN AN HISTORICAL PERSPECTIVE 1-1

- Changing Patterns of Food Consumption 1-3
- Changing Health Concerns 1-4
- Substances in Food 1-10
- Food in Relation to Other Environmental Hazards 1-14
- Scope of Report 1-15
- References 1-16

Chapter 2 THE CURRENT LAW AND ADMINISTRATIVE MECHANISMS OF FOOD SAFETY REGULATION 2-1

- The Role of State Governments 2-3
- The Statutory Classification Scheme 2-5
- Mechanisms for Enforcing Safety Requirements of the Law 2-16
- Problems in Applying the Statute 2-19
- References and Notes 2-22

Chapter 3 ISSUES IN FOOD SAFETY REGULATION: FOUR ILLUSTRATIVE CASES 3-1

- CASE ILLUSTRATION: SACCHARIN 3-2
  - Background 3-2
  - Consumption Data 3-2
  - Risk Assessment of Saccharin and Its Impurities 3-4
  - Assessment of Benefits 3-9
  - Regulatory Considerations 3-12
  - Issues 3-13
- CASE ILLUSTRATION: MERCURY 3-18
  - Background 3-18
  - Assessment of Risks 3-19
  - Assessment of Benefits 3-23
  - Regulatory Considerations 3-24
  - Issues 3-28
- CASE ILLUSTRATION: NITRITES 3-32
  - Background 3-32
  - Assessment of Risks 3-33
  - Assessment of Benefits 3-38
  - Regulatory Considerations 3-39
  - Issues 3-42

CASE ILLUSTRATION: AFLATOXIN 3-45
  Background 3-45
  Assessment of Risks 3-52
  Assessment of Benefits 3-54
  Regulatory Considerations 3-55
  Issues 3-57
FURTHER ISSUES RAISED BY THE FOUR CASE ILLUSTRATIONS 3-61
References and Notes
  Saccharin 3-64
  Mercury 3-65
  Nitrites 3-67
  Aflatoxin 3-70

Chapter 4 CONCEPTUAL TOOLS FOR ASSESSING FOOD SAFETY POLICIES 4-1

Definition of Risks and Benefits 4-1
Acceptability of Risks and Benefits 4-3
Acceptable Risk and the Role of Government 4-5
A Decision Framework for Food Safety Policies 4-8
References 4-18

Chapter 5 TECHNIQUES FOR THE ASSESSMENT OF HEALTH RISKS 5-1

Health Risks from Food Substances 5-1
Overview of Methods for Detecting Health Hazards 5-5
EPIDEMIOLOGY 5-6
  Approaches 5-7
  Establishing Causality 5-11
  Limitation of Epidemiologic Studies 5-12
  Interpreting Epidemiologic Studies 5-16
ANIMAL TESTS 5-17
  Aspects of Methods 5-17
  Estimating Human Risk 5-21
  Interpreting Positive and Negative Results of Animal Tests 5-25
SHORT-TERM TESTS 5-26
  Rationale 5-26
  Specific Tests 5-27
  Interpreting Results from Short-Term Tests 5-31
AN APPROACH TO IDENTIFYING MUTAGENS AND CARCINOGENS 5-33
References 5-36

Chapter 6 CONCEPTS OF ASSESSING BENEFITS 6-1

Types of Benefits 6-1
Assessment of Non-Economic Benefits 6-2
The Context of Assessment 6-10
References 6-13

Chapter 7 INFORMATION, EDUCATION, AND FOOD SAFETY 7-1

- RISK RECOGNITION 7-2
  - Food Consumption Data 7-4
  - Special Risk Groups 7-5
  - Multiple-Source Exposure 7-7
  - Improving Surveillance 7-8
- SCIENTIFIC EXPERTISE IN REGULATION 7-10
- PROVIDING INFORMATION TO THE PUBLIC 7-13
  - Information Devices 7-16
  - The Prospect of Information Strategies 7-20
- PUBLIC PARTICIPATION IN THE REGULATORY PROCESS 7-22
  - Functions of Public Participation 7-22
  - Forms of Public Participation 7-23
- References 7-27

Chapter 8 RANGE OF REGULATORY PROCESSES FOR SAFETY 8-1

- Purposes of Safety Regulation 8-1
- Regulatory Mechanisms 8-3
- Problems in Setting Standards 8-7
- Individualized Screening of Substances 8-10
- Framing a Flexible Policy 8-12

Chapter 9 CURRENT POLICY ISSUES AND RECOMMENDATIONS 9-1

- Need for Reform of Food Law 9-1
- General Characteristics of a System for Food Safety Regulation 9-7
- The Process of Regulatory Action 9-9
- Conclusion 9-31

Chapter 10 OPTIONS FOR REGULATING SACCHARIN IN THE CONTEXT OF THE RECOMMENDATIONS IN CHAPTER 9 10-1

*** MINORITY STATEMENT MS-1

*** SUPPLEMENTARY COMMENTS SC-1

APPENDIXES

Appendix A Saccharin Study and Labeling Act (P.L. 95-203), and Federal Register Notice on Saccharin and Its Salts, April 15, 1977 A-1
Appendix B FDA Use of the Delaney Clause, by Richard A. Merrill* B-1
Appendix BB Regulating Carcinogens in Food: A Legislator's Guide to the Food Safety Provisions of the Federal Food, Drug, and Cosmetic Act, by Richard A. Merrill* BB-1
Appendix C A Comparison of FDA Food Safety Regulation with Federal Regulation of Other Environmental Hazards by Jeffrey Trauberman* C-1
Appendix D International Comparisons of Food Safety Regulation by Knut Ringen* D-1
Appendix E The Decision Framework: An Application to Saccharin E-1
Appendix F Risk Estimates [to Humans from Animal Tests] F-1
Appendix G Discussion of Saccharin Options by Fred P. Abramson (Panel 1) and Richard L. Hall (Committee) * G-1
Appendix H Work of the Committee H-1
Appendix I Glossary G-1

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* Responsibility for the conclusions and content of these Appendixes is solely that of the authors.

COMMITTEE CHAIRMAN'S PREFACE

The issues surrounding the use of food additives have generated considerable controversy during the past few years. In Congress, the debate reached its peak in regard to the possible ban on the use of saccharin. In November 1977 this culminated in the passage of the Saccharin Study and Labeling Act (PL 95-203). The Act requested that the National Academy of Sciences examine the risks and benefits to health of the use of saccharin and consider the more general issues surrounding federal food safety policy.

A coordinating committee and two panels—one to address the saccharin issue and one to examine the general food safety policy—were established by the National Academy of Sciences for this study. The panels and the coordinating committee, which shares responsibility for the content of the report, included biomedical scientists and clinicians with a variety of expertise, lawyers, economists, political scientists, and persons representing the broad public interest. (Membership of these groups is listed in the front of this report.)

Because of the diverse backgrounds and points of view represented, as well as the complexity of the subject, effective communication and consensus building were not easy. Nevertheless, as the chairman of the coordinating committee, I was most gratified to observe the rapidity with which the group developed cohesiveness and members displayed respect for each other's views.

Panel I, whose work focused on saccharin, was organized within the Assembly of Life Sciences. Its report was submitted November 1, 1978. The panel's illustrative case study of saccharin is presented as Part I of the committee's final report.

The basic charge contained in the Act regarding saccharin was that a study be conducted

> "to determine, to the extent feasible—
> (A) the chemical identity of any impurities contained in commercially used saccharin, (B) the toxicity or potential toxicity of any such impurities, including their carcinogenicity or potential carcinogenicity in humans, and (C) the health benefits, if any, to humans resulting from the use of nonnutritive sweeteners in general and saccharin in particular."

The saccharin report presents some conclusions, with varying degrees of certainty. But because of the shortage of time, Panel I made no specific recommendations regarding the use of saccharin. The results of Panel I's discussion about the possible policy in this area are presented in Part 2 of the report, in the context of broader food safety policy.

Panel II, which considered general food safety policy issues, was organized within the Institute of Medicine. Its report—Part 2 of the committee's final report— responds to the charge of the Act that requested

> "a study, based on available information, of (A) current technical capabilities to predict the direct or secondary carcinogenicity or other toxicity in humans of substances which are added to, become a part of, or naturally occur in, food and which have been found to cause cancer in animals; (B) the direct and indirect health benefits and risks to individuals from food which contain carcinogenic or other toxic substances; (C) the existing means of evaluating the risks to health from the carcinogenicity or other toxicity of such substances, the existing means of evaluating the health benefits of foods containing such substances, and the existing statutory authority for, and appropriateness of weighing such risks against such benefits; (D) instances in which requirements to restrict or prohibit the use of such substances do not accord with the relationship between such risks and benefits; and (E) the relationship between existing Federal food regulatory policy and existing Federal regulatory policy applicable to carcinogenic and other toxic substances used as other than foods."

In examining the broad issue of food safety, the panel gave major attention to the problems of food additives and contaminants, less consideration to potentially harmful natural substances, and little or no consideration to the effect of dietary patterns on health. The technical means of evaluating risks and benefits were studied, and an effort was made to delineate clearly their potential usefulness and limitations as a basis for formulating food safety policy.

Ideally, food safety regulation should be simple, efficient, responsive, scientifically based, and would allow for minimal interference with personal freedom and maximal public participation, while providing the greatest possible protection for consumers. These elements were used as reference points in the study, although a perfect system is probably unattainable.

The committee, panel, and staff found the subject of food safety policy to be too complex to deal with comprehensively in the brief time allotted for this study and therefore limited the analyses presented in this report to those issues that could be covered reasonably well. This report supplies some of the data, information, and ideas that are needed for reevaluating national food safety policy, but it should be considered only a first step in this difficult task. Clearly, food safety policy deserves a thorough, thoughtful analysis and periodic review, as it is a vital part of federal efforts towards enhancement of the public's health.

Frederick C. Robbins
Chairman
Coordinating Committee for a Study
on Saccharin and Food Safety Policy
March 1, 1979

PANEL II CHAIRMEN'S PREFACE

Part 2 of the report by the Committee for a Study on Saccharin and Food Safety Policy represents the work of the Coordinating Committee and of Panel II (Food Safety Regulation and Societal Impact); however, individual members of Panel I (Saccharin and Its Impurities) participated—because of their personal interest—in some of the deliberations that led to Part 2. In spite of the broad representation from many diverse professions on the committee and the two panels, it is still important to be aware of the limited competence that a body formed by the National Academy of Sciences/National Research Council can bring to the study of issues that are so deeply embedded in the fabric of our society. The group worked together in an exemplary fashion with great respect of the several disciplines, for each other's viewpoints and areas of expertise.

The time interval of less than one year during which the committee and the panels labored was hardly long enough to gain a common perspective on the problems of a United States food safety policy, to analyze them, and to formulate the principles of a scientifically based—and yet administratively and socially realistic—approach to this important area of our national life.

Public decision-making should be able to adapt to changing conditions in this area in which strongly held values and preferences, as well as economic realities, contrast with incomplete scientific understanding and not always sufficiently documented medical observations. We can obviously neither repeal nor modify the laws of nature but we can presumably adapt the laws of man as we learn to compare more reliably risks and benefits to health in the light of other social considerations.

Since food is such a biological necessity, a policy regarding food safety affects all people no matter what their literacy, intelligence, or education. Hence, the nation's food safety policy must constitute a reasonable societal framework in which individual consumers, industries, and governments can work together with the scientific and medical professions to provide reasonably priced, plentiful, and healthful food. An all-or-none strategy aspiring to unattainable risklessness has under these circumstances little chance of being effective or successful. We should attempt instead to find ordering principles that will allow us to address problems of food safety policy with priorities that reflect both severity of risk and chances for effective remedial action.

Those of use who are concerned with the individual's freedom of choice and with the filtering function ascribed to the marketplace for the elimination of harmful or ineffective products must remember that the cause-effect relations (in addition to being in most instances multifactorial) stretch over an individual's life-time. This is hardly a favorable environment in which to leave the discriminatory task solely to the marketplace or in which we can assume that each individual is operating under conditions of informed consent.

Given the foregoing considerations (and others too long to detail here), the reader of Part 2 ought not to be surprised by the fact that there is a minority opinion and probably more qualifying comments than usual in a National Academy of Sciences report. The wide range of disciplinary backgrounds of the committee membership is only one explanation for this fact. The major reasons lie deeper; they reflect the overall state of the field of nutrition, the scarcity of scientific and established medical knowledge that relates directly to potential regulation, the patchwork of legislation, the historical context in which the Food and Drug Administration operates, the absence of effective techniques in the area of health education, to name just a few.

Hence, we readily confess that this report is at best a modest progress report in the sense that it has tried to inventory in a fairly comprehensive way the food safety issues that beset public policy making under uncertainty. There is no doubt in our minds that this area deserves systematic continued efforts and attention, not only in our organs of government, but in the laboratories, the educational institutions, the industries, and the marketplaces of this nation. This continued effort depends critically upon the education of a new generation of natural and social scientists, of medical specialists and lawyers who are ready to cooperate in bringing to bear their most advanced skills and tools to the management of a contemporary food safety system.

Walter A. Rosenblith
Clifford Grobstein
Co-Chairmen, Panel II, Food Safety
Regulation and Societal Impact

March 1, 1979

SCOPE AND ORGANIZATION OF REPORT

Food safety is a broad subject that impinges on many aspects of modern life. Limited time and resources forced the committee to confine its deliberations to only a small portion of this vast topic. In choosing which areas to cover, the group was guided primarily by the background and requirements of the Saccharin Study and Labeling Act (P.L. 95-203).

Consequently, this report deals primarily not with foods themselves but with components of food, many of which fall in the category of food additives and contaminants. The report devoted special attention to long range health effects of such substances. For purposes of this study, the term "food" excludes drinking water, alcoholic beverages, tobacco, and drugs. Moreover, extensive treatment of general dietary and nutritional factors are beyond the purview of the report, despite their importance to human health. Serious hazards from microbial contamination of foods also will not be considered, because they are relatively well controlled through improved technology and appropriate regulation and inspection of food preparation and storage. Furthermore, foodborne infectious disease is currently responsible for a relatively small percentage of fatalities in the United States, compared with diseases such as cancer and heart disease.

The report opens with an overview of food and health concerns, and closes with a discussion of recommendations aimed at achieving a consistent and comprehensive food safety policy. Chapter 1 describes some of the wide-ranging changes that the food supply in the United States and the health status of the U.S. population have undergone during this century. These changes have raised serious questions about the safety of some substances now found in food. Chapter 2 discusses the current legal basis for regulating substances in food. In describing the evolution of the regulatory system since enactment of the original Food and Drugs Act in 1906, a few of the problems with the present system are noted. The regulatory background forms a basis for the four illustrative cases discussed in Chapter 3. Except for saccharin, the several cases — mercury in fish; nitrites in meat and poultry products; aflatoxins in corn, peanuts and other foods — have not been analyzed in exhaustive detril. Rather, they are presented to draw attention to some of the scientific and regulatory issues that arise in food safety.

Chapter 4 discusses risks, benefits, the concept of acceptable risk, and the characteristics of risks where a government role may be appropriate. The chapter illustrates a possible decision framework that recognizes that risks and benefits may vary among different users of a food substance and with different uses of the substance. The framework also considers the availability of substitutes.

In Chapter 5 the current methods for estimating health risks to humans are described. Epidemiologic studies, animal tests, and short-term tests for detecting mutagens and carcinogens each have advantages and limitations for estimating health risks of substances. Chapter 6 discusses the even more difficult problems associated with assessing physiologic health benefits and perceived benefits. Possible methods for assessing perceived benefits by scaling them relative to each other are considered.

Chapter 7 describes some of the strategies by which regulatory agencies can receive and dispense the kinds of information required for an effective food safety policy. Such a policy requires adequate surveillance and reporting systems to monitor food consumption, food components, and diseases that might be associated with food. Agencies also require information from the scientific community, industry, and consumers. In turn, information about food safety must be conveyed to the public in ways that are useful for making purchasing decisions. Chapter 8 discusses aspects of a flexible regulatory system that would consider a range of options in dealing with foods. Because foods present different types and degrees of risk to different groups of people, regulatory actions other than complete freedom or complete banning may be appropriate and feasible.

Information presented in the first eight chapters is reflected in Chapter 9 in a set of recommendations for a comprehensive regulatory framework for considering present and future issues in food safety. The committee prefers that saccharin be regulated within the new proposed framework. If the Congress decides to enact a special law for saccharin rather than to develop a new food safety regulatory framework, or until such a new regulatory framework is functioning, options for its regulation are considered in Chapter 10 and Appendix G.

Although most committee and panel members agree with the main thrust of this report's recommendations some substantive differences of opinion among 37 people were inevitable on a subject as complex and value-laden as food safety regulation. These differences are presented as a minority statement, followed by supplementary comments following the main body of the report.

Materials that support and amplify various aspects of the study or are too detailed or technical for the main portion of the report, appear as appendixes.

The first four appendixes relate to regulatory issues in the United States and in other countries.

A copy of the Saccharin Study and Labeling Act, P.L. 95-203, which mandated this study, is provided in Appendix A. This appendix also contains a copy of Federal Register No. 73, Volume 42 dated April 15, 1977, containing the FDA proposal for a saccharin ban. In Appendixes B and BB are two papers prepared by Richard Merrill, Daniel Caplin Professor of Law at the University of Virginia School of Law, and formerly Chief Counsel of FDA. The first paper describes the use of the Delaney clause; the second describes the current FDA classification of food substances from a somewhat different viewpoint and in greater detail than does Chapter 2. Appendix C compares the methods and criteria that FDA uses in making food regulatory decisions with the criteria employed by other federal agencies mandated to regulate environmental hazards. Other agencies studied include the Environmental Protection Agency, the Occupational Safety and Health Administration, and the Consumer Products Safety Commission. Appendix D surveys international organizations engaged in food safety and food safety regulatory systems in various industrial countries. The appendix compares these systems with that used in the United States.

Remaining appendixes describe technical matters and the work of the committee. Appendix E uses the case of saccharin as an exercise to illustrate use of the decision framework described in Chapter 4. Appendix F, taken from Part 1 of the study, describes the methods that researchers use in estimating human health risks from animal test data.

The methods that the committee used in carrying out its congressional mandate during the past fifteen months are described in Appendix H. The complex and controversial issues involved in food safety policy engendered lively debate and discussion among a committee whose members came from diverse backgrounds and disciplines. Clearly, not every committee member agrees with every statement in the report; the report represents a general consensus reached after much effort.

To help readers understand technical terms used in this report, a glossary is presented in Appendix I.

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SUMMARY

This report on food safety policy recommends statutory changes in current food law

- to make food safety policy simpler, more flexible, and more comprehensible, and
- to grant to regulatory agencies the discretionary authority they need to deal with the increasingly complex issues of food safety in the light of modern technology.

These recommended changes are balanced by other recommendations that would ensure full consideration by food regulatory agencies

- of the latest and most complete scientific information, and
- of public attitudes and values with respect to levels of safety and individual freedom of choice.

Options for dealing with the specific saccharin issue that gave rise to this study are presented under both present statutory circumstances and the context of the report's recommendations if they were to be adopted.

This report was prepared in response to the "Saccharin Study and Labeling Act," P.L. 95-203, November 23, 1977. The Act required studies on carcinogenic and other toxic substances in food and on the regulation of such food. The committee chairman's preface to the full report quotes the specific charges, and Appendix A of this report (Part 2) reproduces the full text of the Act. A summary of the charges and an indication of where the report discusses them, follow. Briefly, the law requested the National Academy of Sciences to conduct a study, based on available information, of:

A. current technical capabilities to predict carcinogenicity or other toxicity in humans of food additives, contaminants and natural components which have been found to cause cancer in animals [Chapters 3 and 5];

B. health benefits and risks from foods that contain carcinogens or other toxins [Chapters 3 through 6];

C. existing means of evaluating risks and benefits of foods containing such substances [Chapters 3, 5, 6] and existing statutory authority for, and appropriateness of, weighing risks and benefits [Chapters 2, 8, 9];

D. instances in which restriction or prohibition of substances do not accord with relationship between risks and benefits [Chapter 3];

E. relationship between existing federal regulatory policy for carcinogens and toxins in food and non-food areas [Chapter 8, Appendix C].

A further portion of the law required a study that dealt specifically with the technical means of assessing risks and benefits of saccharin and its impurities. In responding to the congressional charge, the National Academy of Sciences formed a Committee for the Study of Saccharin and Food Safety Policy. The technical report on saccharin appeared in November 1978 as Part 1 of the committee's report, under the title Saccharin: Technical Assessment of Risks and Benefits.* Policy issues and options for saccharin are discussed in Chapters 3 and 10, and in Appendixes E and G of the present report, Part 2 of the report of the Committee for the Study of Saccharin and Food Safety Policy.*

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* National Research Council/Institute of Medicine, Committee for a Study on Saccharin and Food Safety Policy. Saccharin: Technical Assessment of Risks and Benefits. Washington, D.C.: National Academy of Sciences, 1978.

In approaching its charge for this report, the committee took into account the shifting patterns of health and disease in the United States and the impact of technology on these patterns, but did not specifically address the much broader issue of nutrition and disease, although the committee recognizes the importance of general dietary factors in causing and preventing disease. Microbial contamination of food was considered beyond the purview of the report, particularly because adequate methods exist for detecting and preventing serious contamination of foods by these agents. Drinking water, drugs, tobacco, and alcohol also were not included.

At the turn of this century, the major causes of illness and death were infectious diseases. Socioeconomic and scientific advances—better nutrition, sanitation measures, immunizations, among others—have so reduced the toll from infectious diseases, that today's major health concerns in the United States and other industrially developed nations are chronic diseases with multiple causes, particularly cardiovascular diseases and cancer.

Industrial development, however, also has brought changes in the human environment, which in recent years have been recognized as possible risks to health. The strongest evidence for environmental-health links for non-infectious diseases has come from studies of populations who have left their country of birth and whose traditional disease patterns have shifted to those of their new host countries within one or two generations, suggesting that environmental factors play an important role. To the extent that a disease is environmentally produced, the prospects for prevention would appear fairly good. Most chronic diseases, however, are caused by a combination of hereditary and environmental factors, and the details of interactions among such factors to produce disease are not yet well understood.

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* Following the body of the report is a minority statement, and supplementary comments submitted by several members of the committee.

The concomitants of industrialization have parallels in the specific area of food. Technical advances have shifted concern about food hazards away from the microbial contamination that produced acute disease soon after exposure. Foodborne infections are now relatively well controlled through improved technology and appropriate regulation and inspection of food preparation and storage. The contemporary concern is with chemicals in small quantities and other hazards introduced by environmental contamination as well as by food production and processing. These substances may form part of a hazardous environmental background contributing to chronic diseases. Many foods are now processed in some way, and the proportion of the American diet composed of such foods has greatly increased. However, even unprocessed, raw foods may contain residues of potentially hazardous substances—pesticides, growth hormones, antibiotics, contaminants from packaging, or other diverse environmental contaminants. Furthermore many edible plants and animals contain naturally-occurring carcinogens or other toxic substances. Examples are spinach which contain nitrates and potatoes which contain potential toxins such as solanine alkaloids. For nitrates, exposure from natural sources far exceeds that resulting from food processing.

Individuals are largely unable to control their exposure to these potential hazards. The substances in question are ubiquitous and information is lacking on which substances are likely to pose a risk and which foods contain these substances in hazardous amounts. Federal regulation of foods has attempted to control exposure to some substances. But public support for this effort, even when it is aimed at preventing a disease as feared as cancer, has become increasingly difficult. The scientific advances that have made possible the detection of contaminants in even smaller quantities, and the animal testing that can give early warning of possible human problems, have sometimes been greeted by the public with skepticism.

Difficulties in Present Food Safety Policy and Some Specific Recommendations

The foundations for present policy were laid in the 1906 Food and Drugs Act, which has been amended several times over the years. The present law accordingly has several "layers," representing successive attempts to deal with then perceived crises. In the view of the committee, the law has become complicated, inflexible, and inconsistent in implementation. Although complex in itself, the law is inadequate to meet changing and increasing problems of food safety. Four cases are examined in Chapter 3 of this report.

- Saccharin - a non-nutritive sweetener added to many foods, for which there is no approved substitute; a low potency carcinogen in animals; some possible health and non-health benefits. Regulatory *status: ban proposed* in 1977, but ban prohibited by Congress pending outcome of the present study.

- Mercury - a contaminant, primarily of fish, which present technology can only partly eliminate; toxic effects on the human nervous system. Regulatory status: permitted concentrations established by FDA now being litigated.

- Nitrites - substances used to cure, color, and preserve meats, for some of which uses there is now no approved substitute, but the greatest human exposure is from nitrates occurring naturally and reduced in the body to nitrites; possibly carcinogens of themselves, nitrites can form substances (nitrosamines) that are high potency carcinogens in animals; nitrites prevent growth of botulism organisms. Regulatory status: unclear; nitrites continue in use, usually at permitted concentrations, although their use is currently under intense scrutiny.

- Aflatoxin - a natural contaminant of such common foods as peanuts, corn, and milk; a proved animal carcinogen of high potency and therefore a suspected human carcinogen. Regulatory status: formal tolerance levels proposed in 1974, pending completion of regulatory requirements; meanwhile, a higher, temporary action level in effect.

An obvious problem illustrated by the four cases is the presence of gaps in scientific information when a regulatory decision needs to be taken. In none of the four cases is current information adequate to remove uncertainty as to appropriate action. We do not know total individual exposure to either aflatoxin or nitrites, we cannot fully evaluate the significance of saccharin as a cancer promoter, and the multiple natural and industrial sources of mercury and its movement through the atmosphere and oceans need more detailed assessment. The problems of scientific risk assessment are discussed in Chapters 5 and 7.

Another major problem presented by the current law is the exclusion, in most cases, of both health and non-health benefits as explicit factors for regulatory consideration. This is especially troublesome when no substitute for a food with a suspected or actual risk exists. Also especially troublesome is the weighing of hard to assess economic and commercial benefits against uncertain or low levels of health hazards. The difficulty of accurately assessing both risks and benefits is a theme that pervades this report (for example, Chapters 4 and 6). Nevertheless, the committee noted that in fact a regulatory agency often tacitly takes benefits into account in making its decision. The committee believes that it is better to have benefits defined, evaluated and openly considered when that is possible. Subjective factors (perceived benefits) also need explicit attention even though they may defy accurate quantification. Nonetheless, the committee reasserts that it should still primarily be risk that triggers government intervention in the food supply and the government must remain cognizant of the centrality of risks in food safety regulation.

Assessment of risks and benefits is useful to organize thinking and is an important part of decision-making, but balanced and informed judgment by responsible authority ultimately is required. Chapter 4 presents a framework for assessing food safety policies. It defines risks and benefits and describes the concept of acceptable risk. The chapter then discusses an appropriate role for government when the public is at risk.

A conceptual framework for food additives is illustrated that permits the consideration of substitutes. It allows discriminating policies for different uses of an additive for different consumer groups. Both health and non-health benefits are considered. The decision framework helps to structure the food safety issue logically, make more explicit those instances in which judgment is required, and to identify areas where more information is needed.

Statutory categorization of foods and food additives currently is confusing, cumbersome and not always clearly related to risks. Contaminants (the probable classification for aflatoxin and mercury) can be regulated through tolerance levels, if their presence "cannot be avoided by good manufacturing practice."* Conceivably, however, mercury could also be classified as a natural constituent of fish whose presence then could not exceed quantities sufficient to be "ordinarily . . . injurious to health."** New food additives and color additives must be tested for safety and approved prior to use, but uses of food ingredients that were established before enactment of the 1958 Food Additive Amendments may be excluded from safety testing if they are generally recognized as safe (GRAS), or if their use was officially sanctioned before 1958. Nitrites in meat are considered to have such prior sanction. Saccharin was classified as GRAS from 1958 to 1972, but rising concern led to its reclassification as a food additive that required safety testing. Substances that induce cancer in animals or humans are prohibited by the Delaney clause from being approved as food additives. Categories in addition to those already mentioned are indirect additives, new animal drugs, and pesticides.

To replace this cumbersome set of categories, the committee recommends a single standard of risk with several broadly defined risk categories. Classification under these categories would establish a range of regulatory possibilities among which the regulatory agency could choose in the light of the best scientific advice, taking into account public attitudes and such benefits as can be assessed.

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*Section 406 of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. Sec. 346.
**Section 402 (a)(1) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. Sec. 342 (a)(1).

Such a system would overcome the significant problem noted in the case examples--the inflexibility of current statutes that operates against developing regulatory measures intermediate between unrestrained use and complete prohibition (see Chapter 8). An example of an intermediate measure might be a phased withdrawal of nitrites as food additives, allowing time for development of acceptable substitutes or changes in consumer food storage practices to control the risk of botulism. The committee recommends that alternative methods for controlling botulism be sought. Flexibility would also permit greater accommodation to the needs and wishes of special populations. For example, pregnant women, because of the extreme sensitivity of the fetus, and children require greater protection against many hazards. The committee finds that the regulatory structure must be flexible and able to respond both to rapid technologic change and to altered public attitudes. However, it emphasizes that regulations also need built-in mechanisms for feedback and evaluation and should be reasonable in terms of compliance and effective enforcement. For instance, in the case of aflatoxin, present procedural requirements make setting regulations unduly time-consuming.

That different regulatory approaches are possible is clear from two reports that were prepared for the committee, one comparing U.S. food safety regulation with regulation of other environmental hazards (Appendix C) and one discussing food safety regulation in other countries (Appendix D).

Components of a Recommended Food Safety Regulation System

The committee believes that reasonable national goals should be established to maximize public health and reduce the risk of carcinogenic and other toxic substances in the average diet of Americans. Characteristics and components of a regulatory system designed to achieve such goals are described in detail in the recommendations (Chapter 9). Among other attributes, the system should offer:

- comprehensiveness, applying to all substances in foods on a uniform and equitable basis, and encouraging use or development of less risky substitutes. This would require abolition of the various classifications in the present statute, and creation of a single standard applicable to all substances.

- discrimination among risk levels, assigning priorities among categories of risks, with emphasis on those that pose the greatest potential hazards. It should apply severe and general constraints only to items involving the greatest, most frequent, and most certain dangers. It should recognize that it is impossible totally to eliminate all risk. As a matter of feasibility, the regulatory process cannot be applied individually to each of the tremendous number of substances in the human diet. The regulatory agency must have a mechanism for setting priorities, so that it can devote its efforts to those substances and combinations that represent the greatest risk, in terms of numbers of persons exposed and seriousness of outcome.

  Without suggesting precise statutory language, the committee proposes that the FDA should be authorized to assign foods to several broadly defined categories, such as high, moderate, and low risk. These categories would not be defined by precise quantitative scientific standards, but would depend on informed judgment. Their function would be to provide a rating scale to help determine regulatory response and priorities.

  > High risk foods or ingredients are materials demonstrated by experience, or suitable scientific testing. to be likely to result in severe (irreversible, incapacitating, or lethal) damage to humans, either in general or in susceptible subpopulations, with appreciable frequency.
  >
  > Moderate risk foods or ingredients are materials that as shown by experience or suitable scientific tests, may cause appreciable harm to humans either in general or in susceptible subpopulations, with sufficient frequency to justify regulatory action designed to modify their use.

Low risk foods or ingredients are those for which there is evidence of some risk, but the risk is neither serious nor frequent enough for placement in the moderate risk category.

Other food Outside of these three categories would be food and food ingredients that, under current knowledge, individually neither pose known risk nor the presumption of any significant risk under reasonable patterns of consumption.

- response of regulatory system based on risk categories. Once the risk of a particular food or food substance has been established both from its potency and exposure level, and a risk category has been assigned, the optimal regulatory strategy must be selected. This should take into account not only the risk of continued use but the risk of limiting or discontinuing use. In some cases, this may mean assessing the objective or perceived benefits so as to weigh them against risk. But, the range of regulatory options for a given risk category should be broad so that the option selected can be carefully matched to the particular case. In many instances an option lying between total discontinuance of use and unrestricted use may be optimal either temporarily or indefinitely. Such options could include restricted distribution, financial disincentives, and others.

  The committee suggests that standard symbols (as have been used to warn of poisonous or radioactive materials) for each risk category may be useful as a means to alert consumers to the need for further information. Such logos would require little space or cost. Depending upon the risk category, further information might be required to be attached to the product or made available on request by the distributor. Experimental use of such logos would be necessary to establish their effectiveness. Whether through logos or other means, the committee believes that consumers must be given the opportunity to play a larger role in food safety decisions. Further research on the most effective means of providing warning and information to consumers is urgently required.

- a greater variety of regulatory and educational approaches, dealing with the complex problem of food safety while avoiding imposition of undue burdens on producers and consumers. Expanding public education and labeling efforts would promote food choices that are in the interest of both the consumer and the public at large. Government-initiated public education campaigns could increase understanding of safe and nutritious diets. Greater involvement of non-governmental groups and advisory committees representing consumers, producers, and professional scientific groups in the decision-making process are recommended.

- regulatory discretion, which is necessary because safety cannot be entirely defined by scientific processes or by the judgment of experts. A reasonable amount of discretion should avoid a far more burdensome and less effective set of rigid prohibitions.

- accountability and jurisdiction. The committee recommends that if the FDA permits the marketing of substances of high risk for limited purposes to subpopulations, with appropriate labeling, it should be required to report its decision in advance to the Secretary of HEW and through the Secretary to the appropriate committees of the Congress.

  Attempts should be made to eliminate problems of overlapping jurisdiction among federal agencies concerned with food safety regulation. With respect to actions or failures to act on the part of other federal agencies that have responsibility for regulating substances in the food supply, that may pose high or moderate risk, the FDA should be authorized to report the matter to the Secretary of HEW.

Besides devoting its efforts to where the risk is greatest, FDA should take all other effective actions to reduce risk where desirable. It should set tolerance levels that encourage or require efforts to develop new technologies to reduce risks. Such technology-forcing tolerance levels could focus on reducing the amount of risky substances in a food, or in seeking substitutes for the risky food or ingredient.

Because the system outlined represents a substantial departure from the current regulatory scheme, a reasonably phased transition with appropriate targets for safety to be achieved cumulatively on a suitable schedule is recommended.

Constraints on Achieving a Comprehensive Food Safety Regulatory System

A comprehensive and flexible regulatory system for food safety will not be easily achieved. High priority must be given to assuring that FDA has the opportunity to employ the most competent staff possible, and to adopt the most effective system of administration. Sound and informed judgment is usually required in making regulatory decisions because definitive knowledge is seldom sufficient to establish either a substance's risk to humans or its true health benefits. As discussed in Chapter 5 and Appendix F, one of the more difficult problems centers on extrapolating the results of toxicologic studies in animals, such as commonly used small rodents, to humans. Although accurate *quantitative* estimates of human risk from animal studies cannot be made, *qualitative* inferences can often be drawn. A substance that is carcinogenic or toxic in other ways in animal experiments is generally considered a potential human hazard. Data from short-term toxicologic tests designed to detect mutagens and possible carcinogens,while contributing additional information are difficult to relate to human risk. Data from epidemiologic studies cannot always be unambiguously interpreted. Translation of the results of such studies into regulatory policy requires judgment. Possible chronic effects of subacute expsoures to toxic substances, inadequacies of data on levels of consumption, differential individual sensitivity that may lead to allergic or other reactions, and diseases associated with food or its constituents are problem areas that demand sound, informed judgment.

The need to improve surveillance and monitoring systems, and to obtain better food consumption data is addressed in Chapter 7. Systematic registries and banking of tissue and food samples might aid in tracking down new environmental health hazards before they become widespread. Surveillance and monitoring systems need to place greater emphasis on total burden from exposure to many hazardous substances rather than considering substances only individually.

Despite the growing need, there is an inadequate supply of expertise in toxicology, epidemiology, and other scientific disciplines needed for investigations, clinical trials, surveillance, benefit assessment, and data analysis from multiple sources. Expertise to evaluate behavioral and attitudinal matters relating to consumer choice of foods is also in extremely short supply. The committee recommends that efforts be made to encourage research and training in these areas.

The committee also recommends greatly expanded efforts in public education and increased public participation in decision-making. Techniques for informing the public about food safety issues need careful study and there appears to be little systematic research underway. Such research could include studies on the types of food labels consumers find most useful and desirable and the experimental use of uniform graphic symbols (logos) to provide information about food contents or to signal the availability of further information. The current law has not emphasized information dissemination as a regulatory food safety strategy. The committee believes that explicit instruction to encourage public education and participation should be given to FDA.

Recommendations Regarding Saccharin Regulation

The specific question of saccharin regulation is taken up in Chapter 10. The committee believes that if Congress takes no further action on saccharin, it will be banned under present law by the Food and Drug Administration. It is the committee's view that its proposed food safety policy would enable FDA to deal with the saccharin issue on a properly discriminating basis, with a wide range of available options, based on an appropriate weighting of saccharin's risks and benefits.

Under the general food safety policy and risk categories proposed in this report, saccharin could belong in either the moderate or high risk category, depending upon the discretion of FDA. In assigning saccharin to a risk category, major considerations are: saccharin is an animal carcinogen (albeit of low potency), and cancers are irreversible and usually serious. Saccharin is widely used, therefore human exposure is extensive. The irreversible nature and severity of the risk and the extent of human exposure, suggest that saccharin be placed in either the moderate or high risk category. The judgment would be influenced by saccharin's apparent low potency as a carcinogen. Whichever category saccharin were assigned to, the regulatory agency would have the option of allowing continued use under specified circumstances. If saccharin were judged to be of high risk, FDA would have the option of banning its use in whole or in part. If not banned, saccharin and all foods to which it is added could be identified by a distinctive logo for the appropriate level of risk, and fully explanatory circulars would be required to be attached or provided on request, depending on the risk level chosen. FDA would also be authorized to take other actions to assure that consumers are alerted to the estimated hazards of saccharin so as to encourage reduced consumption both generally and particularly by subpopulations at greater risk. Those who want or need a non-nutritive sweetener and regard the benefit to them as greater than the risk would still have access to saccharin. Accompanying these steps, research would be encouraged to improve the assessment of both risk and benefit of saccharin, to develop alternatives, and to conduct prospective epidemiologic studies that might in time reduce uncertainty about the consequences of saccharin use. These steps might lead, at the discretion of FDA, to a gradual phasing out of saccharin use over, for example, a three to five year period.

Institution of a comprehensive regulatory system rather than a case-by-case approach to such items as saccharin is favored by the committee. Nonetheless, the committee has outlined a number of options that the Congress could consider if it chooses to deal with saccharin as a discrete problem. The committee provides a full set of options, recognizing that some will not be favored.

These options range from an immediate or phased ban on saccharin for human consumption in any form, to allowing free availability without special labels. Options between these extremes include: exclusion from such a ban of drug formulations and dentifrices; regulation of saccharin as a drug that might be distributed over-the-counter or by prescription; allowing its use as a table-top sweetener, as an interim or long-term measure, but not as a food component; increasing education about saccharin and limiting distribution in order to encourage reduced use by the general population and particularly by groups that are likely to be especially sensitive; allowing general distribution but with various warning labels.

Committee members have differing individual views on these options. All committee members believe it desirable that FDA take steps to educate users to saccharin's risks and to further encourage the search for alternative non-nutritive sweeteners. However, as noted in Chapter 10, most committee members believe that a total immediate ban of saccharin would not be a sound regulatory step at the present time, nor do they favor free distribution of saccharin without special labeling.

Conclusion

The controversy over saccharin use was the impetus for Congress's request for reevaluation of overall U.S. food safety policy. This study suggests that rigidity and complexity of national food safety policy has heightened and confused the saccharin controversy. The committee believes that FDA can better carry out its mandate to protect the public's health if food safety is subject to a less cumbersome and more flexible regulatory policy that is scientifically based and allows full public participation. The Congress could, by delegating more discretionary authority to the FDA, help avoid unduly protracted debates in Congress and undue litigation. A food safety policy, to be effective, must ultimately rest on confidence in sound and informed judgment by officials fully accountable to the public.

Chapter 1

FOOD AND HEALTH IN AN HISTORICAL PERSPECTIVE

Technology has transformed the United States' food supply from the relatively simple product of local farming and home preparation into the complex output of a multibillion dollar industry. In 1928, grocery stores on the average handled fewer than 900 items. 1/ A modern supermarket may offer more than 5,000 food items, most of them processed* to some extent by physical or chemical means. 1, 2/

Processing provides undoubted benefits, such as helping to make foods relatively inexpensive, convenient, attractive, and free of microbiological contamination. However, the increased use of chemicals in all stages of food production may introduce health risks. During the past two decades, people have become aware of the potential dangers of many substances that may be present in foods, including saccharin, pesticide residues, DES (diethylstilbestrol) residues, nitrites, mercury, and aflatoxin. Even trace amounts of a chemical may introduce a health risk to some individuals under particular circumstances. 3/ A major concern is that, if a substance has harmful health effects, they may not be detected or manifested until long after the substance becomes widely used. Moreover, if a substance is a contributing factor to a common disease with a long latent period, such as heart disease or cancer, it may be difficult to establish the connection between the substance and the disease unless the substance's effect is very large.

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*Processing is anything the food industry does to food beyond the simplest preparation for sale.

For centuries people have altered foods, often using chemicals, but never before have the available techniques been as numerous or as widely used. 4-7/ In the past, sailors ate saltpork on long voyages, and people of many nations dried excess meat to prevent spoilage. In the Middle Ages spices and salt became valuable commodities because they preserved food and made it more palatable. Present techniques for treating food include physical processing such as freezing, heating, desiccation, irradiating and vacuum sealing, 7/ and the use of a great variety of chemicals in all stages of modern food production.

Chemicals are added to foods for a variety of reasons. 8, 9/ Some chemicals are added to food to augment or replace physical processing. Others enter at various stages of production and may leave residues in the food. A chemical may serve more than one purpose. For example, nitrites in meats enhance color and flavor and prevent growth of botulism organisms. 10, 11/

Many chemicals prevent microbial growth or other causes of food spoilage. 4, 5/ Baked goods rapidly develop mold in a warm moist environment, but the presence of some of the ingredients commonly seen in packaged bread, such as calcium propionate, inhibits mold growth. Sorbic acid inhibits mold growth in cheese and confections. Antioxidants such as BHA (butylated hydroxyanisole) prevent many foods and cooking oils from turning rancid.

Substances added to food may also increase the food's nutritional value or esthetic appeal. After Vitamin D-fortified milk became common, rickets virtually disappeared as a health problem in the United States. Iodized salt eliminated thyroid goiters as a major health problem in states where natural sources provide inadequate amounts of iodine. Chemicals likewise may increase esthetic desirability by improving food color, flavor, or texture.

Some chemicals that enter food are not intended to become part of the final product. 12, 13/ Pesticides and fertilizers decrease the cost of food production by increasing the yield per acre, but residues may remain on fruits and vegetables. Scientifically formulated diets for animals minimize the costs of producing meat and chicken, but undesirable feed components may appear in the meat. 13/ Even components of packaging materials may find their way into food. 14/

Changing Patterns of Food Consumption

Consumption of processed foods in the United States has increased greatly since 1910, a trend that apparently is continuing. 2, 15, 16, 17/ Individuals in the U.S. also eat a substantial and increasing amount of food outside the home, 18/ which contributes to a consumption pattern that reduces individual control over what is eaten.

A few examples provide a measure of the change. 16/ For citrus fruits, which constitute more than half of fruit consumed in the U.S., fresh use dropped from 32 to 28 pounds annually per capita between 1960 and 1976, whereas processed consumption (expressed as fresh weight), increased from 50 to 90 pounds per capita. Frozen juice accounts for most of this increase. Americans ate about 11 pounds per capita of fresh tomatoes annually throughout the period 1960 to 1976, while canned tomato consumption increased from 44 to 61 pounds per capita.

The pattern for potatoes has been more variable. 15, 16/ Total potato consumption dropped from 180 pounds per person in 1910 to 108 pounds in

1960, and then increased to 117 pounds per person in 1976. Much of the recent increase reflects increased use of frozen french fries at home and by fast food chains.

Other changes in food consumption patterns have occurred. Annual soft drink consumption more than doubled between 1960 and 1976, from the equivalent of 200 eight-ounce bottles per person to 450 eight-ounce bottles. 16/ By 1976, low-calorie or "diet" soft drinks accounted for 11 percent of this total. 19/

Expenditures for food away from home increased from one quarter of the food budget 20 years ago to more than one-third of an approximately $200 billion food budget in 1977. 18/ Between 1965 and 1976 fast food establishments increased their share of away-from-home food expenditures from 10 percent to 25 percent.

Changing Health Concerns

Public concern about health effects of foods parallels a change in general health concern which has been moving away from acute infectious diseases and toward chronic diseases with long latent periods. 20, 21/ In 1900, when life expectancy at birth was 47 years, pneumonia and influenza were the leading causes of death, followed by tuberculosis and combined diarrhea and enteritis; together these accounted for 550 deaths per 100,000 population, or about 30 percent of total mortality. Heart disease was fourth, killing 137 people annually per 100,000 population, and cerebrovascular disease was fifth. Cancer was eighth, accounting for 64 deaths per 100,000. By 1940, the three leading causes of death had achieved their present position: heart disease first, cancer second, and cerebrovascular disease third.

In 1976, with life expectancy exceeding 70 years, heart disease accounted for 337 deaths per 100,000 population; cancer accounted for 176; and cerebrovascular disease 88, out of a total of 890. These three categories of diseases accounted for 68 percent of total deaths; influenza and pneumonia accounted for only 3 percent. 22/

Although researchers can easily show that foods prepared for the retail market are free of serious microbiological contamination, they cannot so easily show that consumption of processed foods, or of raw foods produced under modern conditions, does not cause or exacerbate chronic health problems. Processed foods are now relatively free of serious microbial contamination and most food poisoning from infectious agents results from the actions of individuals after food leaves the manufacturer. 23/ For example, most cases of botulism occur from improper home canning, especially of vegetables. 24, 25/ Of 602 attributable outbreaks* of foodborne botulism in the U.S. between 1899 and 1976, 22 percent of those before 1930 were attributed to commercial processing, but since 1930 less than 4 percent were caused by commercial processing.

Since many interacting factors contribute to the incidence of prevalent chronic diseases, it is difficult to correlate changes in diet with changes in disease prevalence. 20, 26-29/ However, food substances may play a role in many current health problems that vary widely in incidence and in seriousness. Effects may range from minor reversible allergic reactions 30/ or

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*The Center for Disease Control defines a "botulism outbreak" as one or more cases attributable to a single cause. (The Center generally defines "outbreak" as two or more cases attributable to a single cause). In 1976, processors were not responsible for any of the dozen botulism outbreaks in the U.S., whose causes were known. Commercial ham, bacon, and sausages have not been known to be associated with botulism in the U.S. during the past 10 years.

"Chinese restaurant syndrome" induced by monosodium glutamate (MSG), 31/ to serious neurologic malfunction resulting from consuming mercury-contaminated fish, 32/ to other life-threatening diseases. There is particular concern about health effects that may be serious, permanent, and delayed in onset, and whose causes may be difficult to establish. Cancer, developmental abnormalities, and genetic damage are in this category of special concern.

As a debilitating and often painful class of diseases with high fatality rates, cancer receives a heavy share of public health concern. Cancer is not a single disease, but a group of diseases found worldwide that share many biological characteristics. 19, 33, 34/ Each type of cancer has its own rate of occurrence within a given population, but rates vary among population groups. All cancers are similar in that they apparently occur when body cells begin to multiply rapidly without the usual biological restraints, and eventually spread to distant parts of the body. Most common types of cancer, such as those of the lung or breast, seem to develop over periods of 10 to 25 years.

Current theories hold that most cancers arise from an interaction of genetic and environmental factors. In specific areas the interactive effect is striking, such as the increased incidence of skin cancer seen when persons with the genetic disease xeroderma pigmentosa are exposed to ultraviolet light. 35/ The latter disease seems to be associated with faulty DNA repair. Several types of cancer, accounting for only a few percent of the total, are attributed primarily to heredity.

Recent increased public concern with environmental carcinogens notwithstanding, incidence and mortality rates for most cancers in the U.S. population have remained relatively constant during the past 35 to 45 years. 34, 36-38/ Figure 1-1 shows mortality time trends for the most common cancer sites. Notable changes appear in the large increase of lung cancer in males—attributable primarily to smoking—and decreases of stomach cancer in both sexes and of uterine cancer. Lung cancer accounts for the major part of the increased cancer mortality in white males between 1950 and 1973-1974. 37/

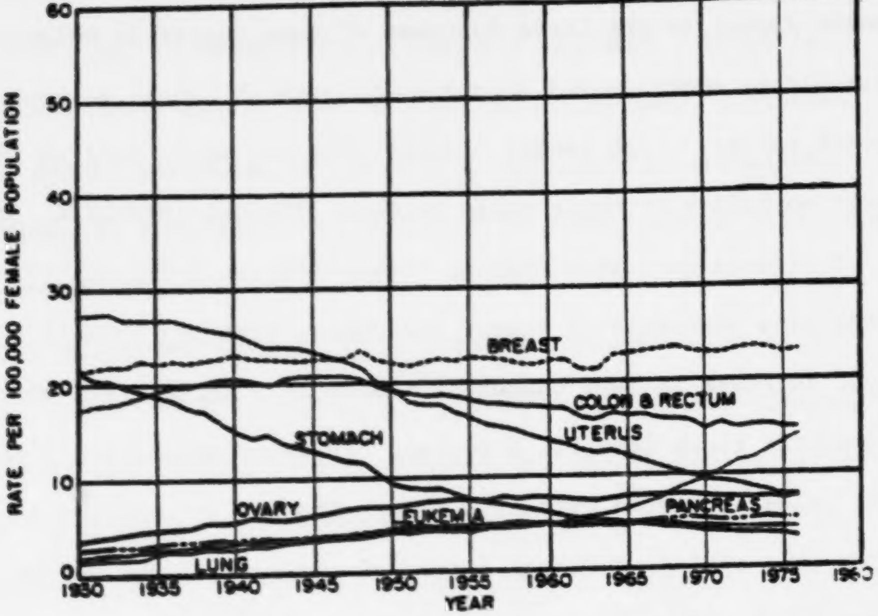
Incidence data show similar trends (Figure 1-2). 36, 37/ The most recent data available on cancer incidence, covering 1973-1976, show an annual increase in lung cancer incidence of 8 percent for white females, 10 percent for black females, 1 percent for white males, and 4 percent for black males, compared with 1970 data. Stomach cancers continued to decline during this period, although cancer of the body of the uterus seems to have increased by about the same percentage as female lung cancers.

Overall, recent data provide little support for the notion that cancer incidence is rapidly rising as a result of environmental pollution or food content. The presence of long latent periods, however, restrains too optimistic an interpretation of available data.

Another area receiving special attention is in utero exposure to hazardous substances, since substances that do not endanger an adult may permanently damage the much more sensitive fetus. Pregnant women in Japan who ate fish contaminated with methylmercury were not themselves seriously affected, but gave birth to children with an increased incidence of cerebral palsy. 39/ Delayed cancer incidence from exposures in utero is a possibility that cannot be ignored in the current state of knowledge because of the long latent period of cancer induction and because too little is known about interactions among several substances in the causation of human cancer.

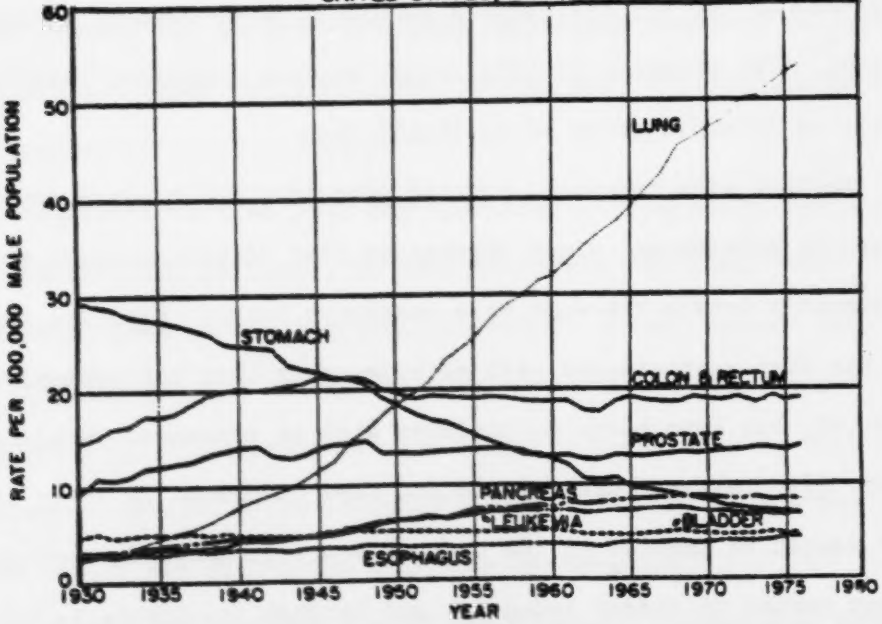
Figure 1-1. Cancer death rates in the United States by disease site, 1930-1976.

FEMALE CANCER DEATH RATES* BY SITE
UNITED STATES, 1930-1976



*Rate for the female population standardized for age on the 1940 U. S. population. Sources of Data: National Vital Statistics Division and Bureau of the Census, United States.

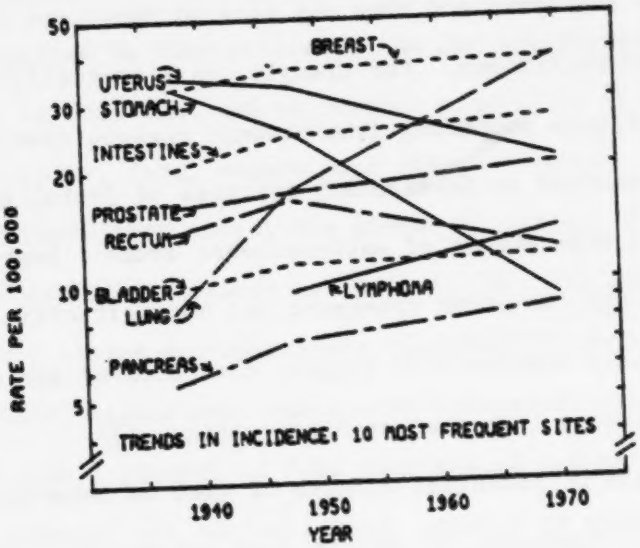
MALE CANCER DEATH RATES* BY SITE
UNITED STATES, 1930-1976



*Rate for the male population standardized for age on the 1940 U. S. population. Sources of Data: National Vital Statistics Division and Bureau of the Census, United States.

Source: American Cancer Society. Cancer Facts and Figures 1979, p. 8. New York: American Cancer Society, 1978.

Figure 1-2. Trends in incidence rates of cancer in the United States—ten most frequent sites.



These data are age-adjusted to the 1950 United States population and are based on three surveys that covered the years 1937-1939, 1947-1948, and 1969-1971.

Source: Devesa, S. S. and D. T. Silverman. Cancer incidence and mortality trends in the United States: 1935-1974. J. Natl. Cancer Inst. 60:545-571, 1978.

There has been rising interest recently in the effects of diet on the central nervous system, memory, and behavior. Some studies in this area suggest that certain aspects of brain function may depend partially on the intake of particular nutrients, such as choline and lecithin. 40-43/ These are precursors of substances that are involved in transmitting nerve impulses in the brain and they may play an important role in various neurologic conditions. For example, in a controlled clinical study, 9 of 20 patients suffering from chronic tardive dyskinesia (a disease characterized by involuntary twitches of facial muscles that is a frequent side effect of antipsychotic drugs), improved when they received choline. 41/ No other treatment had been effective for this disease. Preliminary reports also suggest that choline may ameliorate certain types of memory loss that accompany aging. 43/

Another example of potential effects of diet on behavior is the hypothesis that the ingestion of certain food substances contributes to hyperkinesis in children, leading to the suggestion that children should have a diet free of particular chemicals. 44/ To date the hypothesis has not been confirmed, 45/ but there is suggestive evidence that a subpopulation of preschool children may benefit from a diet free of certain coloring ingredients. 46/

Substances in Food

For regulatory purposes, the law generally classifies substances in foods by their "route of entry,"—how and why they entered the food. 47/ The four major classes of food substances are:

- Natural constituents of food, such as alkaloids.

- Direct ingredients.* These substances are added directly to food to achieve a technical function such as preservation. They usually are intended to remain in the final product. Examples are nitrites.
- Indirect ingredients. These substances, such as those derived from packaging material, are intentionally used in food production, but are not intended to be present in the food when it is consumed.
- Contaminants, such as PCB's (polychlorinated biphenyls).

These categories as they relate to the law are discussed in Chapter 2.

Substances in food also may be roughly classified from a nutritional viewpoint as proteins, fats, sugars, and starches—often called macronutrients. Macronutrients constitute almost 97 percent of the dry weight of naturally occurring substances in food. 4, 48/ The remaining approximately 3 percent, called micronutrients, includes vitamins, minerals, and other nutritionally significant substances present in relatively small amounts. Less than 1 percent of food consists of non-nutrient substances, which are the primary, but not exclusive, concern of this report. Their effects on human health may be positive, neutral, or negative.

Substances in foods number in the thousands, and include both synthetic and naturally occurring chemicals. 49/ In fact, foods are made up of chemicals. Organisms do not distinguish physiologically between synthetic and natural substances as such, or between substances introduced into the food supply intentionally or accidentally, directly or indirectly. A given substance is just as safe or just as toxic whether it is a natural component or is synthesized in a laboratory. However, the public and regulatory agencies tend to be more concerned with chemicals that are added to food because those usually are more readily controlled and because they are not natural constituents of the food.

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*In legal terminology, this group includes food additives and various other substances. To avoid confusion with legal meanings, this chapter uses the term "direct ingredient."

Edible plants and animals may contain naturally occurring hazardous substances, some of which are carcinogenic in animal tests, or are toxic in other ways. 48/ Poisonous mushrooms and plants with hallucinogens are familiar examples. Processors may no longer add the two natural substances, coumarin and safrole, to food because they cause liver damage in animals. 50/ Even so familiar a food as the potato is a complex chemical aggregate with 150 distinct chemical entities, among them potential toxins such as tannins, nitrate, arsenic, oxalic acid, and solanine alkaloids. 48/ The number of unidentified natural substances probably exceeds the number that already are known.

The use of direct ingredients has increased as processed food consumption has increased. There are now about 2,000 such substances, which function as preservatives, texture agents, colors, flavors and flavor enhancers, and in other ways. 9/ They include single chemicals, such as ordinary table salt, as well as complex mixtures, such as vanilla extract. Between 1960 and 1970, the total amount of these substances used by food processors appears to have approximately doubled. 4, 51, 52/ However, dependable data are sparse because the need for systematically collecting accurate information about use of direct ingredients has been recognized only recently. 53/

Although their total number is large, a relatively small number of direct ingredients account for the bulk of these materials in commercially prepared foods. In the U.S. the four most abundantly used direct ingredients per capita in 1975, based on data supplied by major manufacturers, were nutrient substances: sucrose (table sugar), 35 pounds; sodium chloride (table salt), 10 pounds; corn syrup, 10 pounds; and dextrose, 2 pounds. 52/ These amounts exclude substances added directly by consumers themselves, so the data do not show total use. For example, total per capita consumption of table sugar is closer to 100 pounds per year than to 35 pounds.

In 1970, the last year with completely tabulated data, Americans consumed a total of about 10 pounds per capita of other direct ingredients, with the 30 most used substances accounting for about 9 pounds. However, the amount of a substance ingested by weight is not necessarily related to its potential danger or to the attention it receives. For instance, neither saccharin nor sodium nitrite, two suspected human carcinogens, is among the top 55 such substances in yearly per capita use, although both have received extensive attention in recent years.

New questions about other types of potentially toxic substances arise in part because of the increasing sensitivity of methods to detect miniscule quantities of chemicals in food. 54/ Some materials whose presence in food was undetectable 20 years ago are now measurable in parts per billion or parts per trillion. This sensitivity presents both opportunities and problems, because the mere presence of a particular chemical is not necessarily cause for alarm. The extent of health risks posed by the exceedingly low concentrations at which substances can now be detected is not known. Yet the improved analytical ability allows the possibility of permitting by law only very low concentrations of potentially hazardous substances in foods.

Food in Relation to Other Environmental Hazards

The modern environment contains many potentially hazardous substances which may be present in the water and air, as well as in foods. Factors in these different areas may interact in producing health effects, although they are usually considered and regulated independently.

While people may be willing to accept unwanted side effects in drugs that accomplish a particular purpose, and the existence of occupational hazards, they may be less willing to accept the idea that food is not totally safe. Individuals can make choices about which foods to eat and by having available, and consuming, a wide variety of foods, can much more easily give up a particular food item. Therefore, a more stringent standard of safety may be appropriate for foods than for other environmental hazards.

Now that foods in the U.S. are relatively free of contamination by harmful microorganisms, the major effect of food on individual health probably depends more on nutritional quality than on small amounts of hazardous substances that may be present. Heart disease, certain cancers, hypertension, and adult-onset diabetes have been linked to diet through epidemiologic studies, including studies of people who have moved from a culture with one set of dietary habits to an area with very different dietary customs. For example, Japanese who migrate to the U.S. have quite different incidences of some diseases than Japanese in Japan. 26-29/ Although associations between diet and disease exist, it is particularly difficult either to infer that diet causes the disease, or to determine which aspects of the diet are most important. After nutritional factors, contaminants might be responsible for the second largest overall effect of food on health. Ingredients purposely added to foods would probably have the least effect.

However, the most influential health factor--nutrition--is not easily regulated, because it depends primarily on individual eating patterns. While laws and regulations can minimize contaminants in foods, ingredients that are added directly and purposely to foods are most easily controlled. This latter group receives the greatest attention.

Scope of Report

This report is concerned primarily with non-nutrient components of food, and especially with potential long range health effects of such substances. While recognizing their importance to health, the report will not discuss general dietary and nutritional factors. Serious hazards from microbial contamination of foods also will not be considered, because they are relatively well controlled through improved technology and appropriate regulation and inspection of food preparation and storage. Foodborne infectious disease is currently responsible for a relatively small percentage of fatalities in the United States, compared with diseases such as cancer and heart disease. The report does not discuss drinking water, alcoholic beverages, tobacco, or drugs.

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Chapter 2

THE CURRENT LAW AND ADMINISTRATIVE MECHANISMS OF FOOD SAFETY REGULATION*

Since 1906, the federal government has led efforts to assure the safety of food manufactured and sold in the United States. Before enactment of the original Food and Drugs Act 1/ that year, governmental measures to assure food safety were largely limited to state laws that prohibited the sale of impure foods and to some state regulatory acts that did not apply to out-of-state manufacturers. For many years, advocates of a strong federal role were unable to persuade the Congress to pass comprehensive legislation to assure food purity, but in 1906 revelations about unsanitary and deceptive commercial practices induced overwhelming public pressure for federal regulation. Probably the best known series of revelations was in The Jungle by Upton Sinclair, a sensational exposé of meat packing practices, which was published five months before the passage of the law.

Many of today's principles of federal food safety regulation were articulated in the 1906 law. These principles include regulatory authority to prohibit deceptive labeling, the presence in food of material esthetically unfit for human consumption, and the use in food of "poisonous or deleterious" substances that may render the food "injurious to health." Food that fails to meet the safety requirements established in the statute is considered "adulterated." Food that is deceptively labeled or packaged is considered "misbranded." Sometimes these statutory principles have been applied to specific foods through regulations, which in turn are subject to judicial review. Adulterated or misbranded food may not enter interstate commerce, and violators of this restriction face criminal and civil sanctions.

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*Early in the study, Richard A. Merrill briefed the committee on the food safety provisions of the Federal Food, Drug, and Cosmetic Act. His paper, "Regulating Carcinogens in Food: A Legislator's Guide to the Food Safety Provisions of the Federal Food, Drug, and Cosmetic Act," which describes food safety regulation under current law, is Appendix B of this report. Appendix D describes food safety regulation in selected foreign countries. Appendix C compares federal food safety regulation with other types of federal safety regulation.

The Congress has amended the original law many times. The Federal Food, Drug, and Cosmetic Act of 1938 replaced the 1906 act, strengthening and extending the food adulteration and labeling provisions, creating more stringent requirements for drugs, and authorizing regulation of cosmetics and medical devices. 2/ In 1958, the Food Additives Amendment was enacted to require premarket testing and approval for new uses of food additives. 3/ The Color Additive Amendments of 1960 applied similar requirements to the use of coloring agents. 4/ In 1968, statutory requirements for the use of new animal drugs in food-producing animals were consolidated. 5/ These and other changes have made the food safety provisions of today's Federal Food, Drug, and Cosmetic Act a confusing weave of legal standards, classifications, and requirements.

Enforcement of the Food, Drug, and Cosmetic Act is the primary responsibility of the Food and Drug Administration (FDA). In fiscal 1978, this agency of the Department of Health, Education, and Welfare spent approximately $81 million on food safety. 6/ Within FDA, the Bureau of Foods has major responsibility for food safety. FDA prepares regulations, examines product samples, inspects establishments, issues publications, replies to consumer inquiries, takes enforcement actions, and exercises other duties as a regulatory agency. Because of limited resources in the food safety area and the presence of many thousands of food substances and products, the agency necessarily sets priorities and cannot give equal attention to all issues. It must rely in part on industry cooperation in conducting scientific tests and complying with regulations.

FDA and the Department of Agriculture (USDA) have overlapping jurisdictions in regulating certain foods, such as meat and poultry.

The Role of State Governments

Although the federal government controls products in interstate commerce, state and local governments are closer to the marketplace and can act more quickly to contain problems within their jurisdictions. Federal and state authority originate in different constitutional powers. The federal government is empowered by the Constitution to exercise authority over interstate commerce, and definitions of interstate commerce have been expanded to embrace nearly all food products. State food safety laws and activities are an exercise of the states' power to protect health and safety. Federal regulation in a particular food safety matter may override state regulation if the Congress explicitly has declared that federal requirements are exclusive, or if federal and state requirements are contradictory. 7/

There are three types of state statutory authority:

- General public health laws entrusting broad powers in state and local agencies for the protection of the public's health.
- General legislation dealing with adulteration, misbranding, or false advertising, patterned after federal food laws enacted at various times.
- Enactments that deal with limited aspects of consumer protection, such as regulation of establishments or specific products.

According to the Association of Food and Drug Officials, 42 states and the District of Columbia have adopted some version of the Model State Uniform Food, Drug, and Cosmetic Act. 8/ This legislation is based on and partly identical to the Federal Food, Drug, and Cosmetic Act of 1938. Eight states still have food legislation based on the 1906 Food and Drugs Act. 9/ Approximately 29 states have adopted versions of the 1958 Food Additives Amendment, the 1960 Color Additive Amendments, and the 1954 amendments to the federal act concerning pesticide residues in foods; 10/ most of these 29 states have specific regulations implementing these provisions.

Although the states generally follow the federal lead in defining adulterants in food, state requirements occasionally differ from federal standards. Michigan has established a limit on polybrominated biphenyl

(PBB) residues below the federal limit, 11/ and Arizona has higher limits than FDA for aflatoxin in cottonseed intended for use as feed for non-lactating animals. 12/ Forty-five states have authority to embargo or detain goods suspected of being adulterated or misbranded, 13/ but FDA does not.

The bulk of state expenditures on food safety support inspection and analysis, usually for the detection of bacteriologic contaminants but sometimes for detection of restricted additives. In the aggregate, states spend about $65 million annually on food safety. 14/

Priorities for expenditure of funds apparently vary widely from state to state, although expenditures in the milk and dairy area are relatively high in all states. Besides wanting to prevent the transmission of disease, states also may want to prevent out-of-state dairy products from competing with the products of in-state dairies.

Local jurisdictions, through county or municipal health departments, also exercise authority over food safety. This authority primarily covers retail stores and food service establishments, such as restaurants.

The Statutory Classification Scheme

The food safety provisions of the Federal Food, Drug, and Cosmetic Act implicitly categorize food substances based on their route of entry into the food supply. For purposes of analysis, four major categories may be identified 15/ (although other taxonomies are possible). These are (1) raw agricultural commodities and their natural constituents, such as meat, canned corn, solanine in potatoes, oxalic acid in rhubarb, and nitrates in spinach; (2) contaminants, such as aflatoxin in corn and peanuts; (3) ingredients directly added to foods during manufacture or processing, such as saccharin in soft drinks; and (4) indirect ingredients used in agriculture, manufacture, or storage that leave residues in foods, such as acrylonitrile in beverage containers. These four categories are not entirely discrete, so that apples, for example, may be a raw agricultural commodity or may be an ingredient directly added to applesauce. In each category, it is the individual food substance, such as saccharin, rather than the marketed food product, such as a particular brand of diet soft drinks, that is subject to general regulation under the safety provisions of the Act.

A detailed discussion of the regulatory framework for each food category is unnecessary for purposes of this report, but some important differences in the way the categories are now regulated under federal law need to be highlighted. Of special relevance is the extent to which FDA may consider benefits as well as risks associated with a substance in deciding what regulatory action to take.

Raw Agricultural Commodities and Their Natural Constituents

Under Section 402 of the present Act, raw agricultural commodities and their constituents are permitted in the food supply, but may not be present in a food in sufficient quantity to be "ordinarily . . . injurious to health." By contrast, under the same section of the law, substances that are "added" cause a food to be adulterated if they "may render [the food] injurious to health"—a standard that is more stringent. 16/ Subtle differences in interpretation of such phrases and terms, while not vital to this discussion, emphasize that the regulatory complexity of the classification scheme leads to confusion.

If FDA concludes that a poisonous or deleterious natural constituent adulterates a particular food, the agency may initiate court enforcement proceedings against its distribution. The Act neither directs nor forbids FDA to consider the benefits of a natural constituent--or of the food containing it--in deciding whether to take action against it. It can be assumed, however, that FDA would not seek a court order that would have the effect of banning a widely popular, long-used, economically and nutritionally important food, unless the food posed a risk of considerable magnitude.

Contaminants

Contaminants, such as aflatoxin on corn and peanuts, are the second major category of food substances. Under the law, these are considered "added" poisonous or deleterious substances because they are not inherent constituents of food. For an added "poisonous or deleterious" substance that is "required in the production" of the food or "cannot be avoided by good manufacturing practice," Section 406 of the Act authorizes FDA to issue regulations that set tolerance levels. 17/ These tolerances are maximum concentrations of contaminants permitted in foods. The law directs FDA to set these tolerances at levels that are deemed "necessary for the protection of public health."

In developing a tolerance level for an unavoidable added contaminant, the Act requires consideration of the extent of a substance's unavoidability in the food. In practice, FDA evaluates the costs and technologic capability of reducing or eliminating the substance, demonstrating that consideration of some benefits now is a factor in the regulation of these substances.

A problem of definition arises with the term "added." The Act itself does not define this term. FDA maintains that a contaminant, such as mercury in fish, is "added" through environmental processes if it is not inherent in the food, whether or not human activity played a part. 18/ Some courts in the past have adopted the FDA position and others have disagreed with it. 19/*

As a matter of administrative practice, FDA usually establishes an "action level" rather than a formal tolerance for a contaminant. Action levels are a regulatory device used by FDA as an alternative to tolerance levels when information about risks is very tentative, when quick regulatory action appears necessary, when technologic or industrial changes are expected to reduce contamination in the near future, or possibly when a long-term regulatory approach has not yet been decided on. An action level constitutes a warning to food producers that food lots containing quantities of the contaminant exceeding the action level will be subject to regulatory action. In short, it is a statement of enforcement policy, not a conclusive rule of adulteration.

FDA sets an action level without holding formal hearings or undertaking the other public procedures involved in setting tolerances. FDA publishes notice of an action level in the Federal Register, which is effective immediately. Public comments may then be submitted, on the basis of which the action level conceivably could be changed, but no further agency response is usually planned.

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*For a detailed discussion of the statutory provisions on contaminants, see Appendix B, pages 22-34.

Action levels thus offer the advantages of quick promulgation, whereas setting tolerances requires very cumbersome administrative procedures. 20/ But over a long time, action levels might be disadvantageous to FDA because courts easily can disregard them (as has happened in two cases involving action levels for aflatoxin and mercury), whereas tolerance levels must be sustained in court if they are supported by substantial evidence and were established through proper procedures. Action levels also may be less desirable as a routine approach because they conceivably could be set without FDA officials' becoming apprised of all relevant factors and interested viewpoints.

Direct Ingredients

Substances directly added to foods during manufacture or processing are the third major category of food substances under the Act. This category includes direct food additives and color additives. In this discussion, the term "food additive" is used in its legal rather than its colloquial sense. Under the Act, the term "food additive" is defined to exclude food ingredients that are generally recognized as safe (GRAS) by experts and so-called prior sanctioned substances that FDA or the Department of Agriculture (USDA) had approved for use before enactment of the 1958 Food Additives Amendment. 21/

Section 409 of the statute requires food additives to be tested for "safety" and approved prior to use. A manufacturer seeking approval of a food additive use must submit a petition to FDA that includes the results of various safety tests. 22/ The regulatory response is an order either rejecting the petition or approving use of the additive under stated conditions and levels of use.

Under the "general safety clause" of Section 409, a food additive may be approved only if it is found to be safe for its intended use. 23/ The law does not define "safety," but the legislative history indicates that the Congress used this term to mean a "reasonable certainty" that no harm would result from use of the additive. Thus, if a food additive poses a reasonable possibility of harm under particular conditions or levels of use, such uses may not be approved, regardless of the benefits offered.

A well-known proviso to the general safety clause is the "Delaney clause," which provides:

> That no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal . . . 24/

The scope of the Delaney clause is limited: it does not apply to food substances that are raw agricultural commodities and their natural constituents, contaminants, or ingredients that are generally recognized as safe or were officially approved for use before 1958. The Delaney clause requires the exercise of scientific judgment. It does not apply to substances that are found to be carcinogenic only in inappropriate or inadequately conducted animal experiments, or are otherwise indicated to be carcinogenic only in experiments with results that scientists interpret as inconclusive. Whether the clause prohibits the use of substances that are not cancer initiators, but affect the course of the disease, is not clear. Because all these limitations involve both legal and scientific judgment, arguments often can be made to render the clause inapplicable to a particular substance. The Delaney clause has been invoked directly for only six substances and thus far has resulted in the banning of only two substances. 25/*

Repeal or amendment of the Delaney clause appeals to some people who are concerned that it unduly restricts freedom and could prevent use of additives offering substantial health, economic, or esthetic benefits. 26/ Others find the clause an important guard against cancer. 27/

The practical effect of changing or eliminating the Delaney clause without revising the rest of Section 409 is questionable; the general safety clause still would remain and it is doubtful that any known carcinogen could be deemed "safe" for direct addition to food. However, the Delaney clause is not necessarily redundant to the general safety clause. The existence of a strongly worded anti-cancer provision may make regulators and courts who implement or interpret the law extremely wary of suspected or possible carcinogens. The clause also may deter industry from manufacturing and proposing new additives that not only are subject to costly and time-consuming experiments but also must meet a difficult statutory test. Further, the clause is explicit in prohibiting carcinogenic food additives regardless of the level of risk (or, as is the case with the general safety clause, regardless of the benefits). The clause also is explicit in providing in legislation that known animal carcinogens, as well as known human carcinogens, are unacceptable as food additives.

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* Appendix B contains "FDA Use of the Delaney Clause," by Richard A. Merrill.

Although Section 409 does not explicitly say what is meant by "safety," it establishes some criteria for determining safety. These include probable consumption levels, accumulated effects of components of the additive and related substances in the diet, and safety factors used to apply animal test data to humans. 28/ The language of the Act does not clearly recognize that there is no food that is absolutely safe for all people in any amount.

In deciding whether to approve a proposed additive, FDA also is required to ascertain that the substance achieves its intended effect, such as flavoring, texturing, or preserving. 29/ The law does not otherwise require or prohibit FDA assessment of the health, economic, or other benefits of the proposed additive.

Proposals and approvals for new direct additives are not numerous, possibly because of a lack of a large public constituency pressuring for approval, the high costs of animal tests, and the fact that new additives that merely duplicate the functions of additives already in use would be unnecessary.

The GRAS exemption is not absolute. If FDA learns of hazards posed by a GRAS substance, the substance may lose GRAS status and become subject to regulation as a food additive as defined in the law. There is no authoritative listing of the thousands of GRAS substances in use, although FDA does maintain a non-exhaustive list of substances that it considers to be GRAS. 30/ There is also no list of prior sanction uses, mainly because of the past inadequacy of agency records. Therefore, determining whether a substance was prior sanctioned, and for what uses, is often difficult. For example, a pre-1958 letter to a manufacturer from an FDA or USDA official recognizing industry use of a substance may or may not constitute prior sanctioning, depending on the wording and circumstances of the letter. Both GRAS and prior sanctioned substances are subject to the adulteration provisions of the Act.

Like food additives, color additives must be approved as safe before being marketed. Color additives used before enactment of the 1960 Color Additive Amendments were placed on a provisional list so that their use did not have to be immediately suspended pending expensive and time-consuming animal tests. The provisional list is currently being phased out, and colors that are approved are placed on a permanent list, while those that are disapproved are banned ("delisted"). A statutory anti-cancer requirement virtually identical to the original Delaney clause applies to permanently listed color additives used in foods. 31/ There are no GRAS or prior sanction exemptions for color additives.

Indirect Ingredients

The final major category of food substances under the Act consists of chemical substances used in agriculture, manufacture, or storage that leave residues in foods. This category embraces indirect additives and indirect GRAS and prior sanctioned substances, pesticide residues, and new animal drugs.

Processing and Packaging Ingredients These are materials in packages or on other surfaces that contact food during processing, other stages of manufacturing, or storing; such materials are non-food substances that migrate or can reasonably be expected to migrate into food in some small quantities. They are regulated under Section 409 of the Act under the same criteria that apply to direct food additives. 32/

An important aspect of regulating indirect additives is the problem of confirming migration of substances into food. In 1977, in prohibiting the use of acrylonitrile copolymers to make beverage containers, FDA adopted a mathematical diffusion model to predict migration. The agency asserted that it need not rely solely on chemical analysis to ascertain the presence of components of packaging material in food. 33/ Because the statutory definition of food additives embraces any substance that "may reasonably be expected" to migrate when used as intended, FDA contends that acrylonitrile need not actually be found in beverages through chemical analysis to be classified as a food additive. Industrial parties contend that a mathematical model is legally insufficient to establish migration under Section 409 of the Act.

The adequacy of a mathematical model to bring manufacturing substances within the safety requirements of Section 409 is potentially an important issue with wide applicability. Almost any substance used in manufacturing, packaging, distributing, or storing food could be expected to migrate in some minute quantity into the food product. The law does not mandate FDA to ascertain the extent of migration, only its occurrence. If migration occurs, the substance will require premarket testing and approval unless it is GRAS at that level or prior sanctioned. In issuing a regulation governing use of the additive, however, FDA can consider the health effects at different levels of migration based on conditions of use, unless the substance has been found to induce cancer in humans or animals.

Although it has banned acrylonitrile copolymers from use in beverage containers, the agency still permits other uses of acrylonitrile copolymers in limited concentrations by the food industry. 34/ Special attention for beverage containers might be justified by the relatively large consumption of beverages compared with other food products.

There appear to be alternative ways, under the present law, in which FDA could implement the Delaney clause with respect to indirect food additives. For example, in the analogous situation of new animal drugs (discussed below), FDA uses a risk assessment method to determine permissible levels of residues in feed. This method, explained in Appendix F, involves postulating an "acceptable" level of risk and then extrapolating from known dose-response data to determine the amount of animal drug residues that will produce this level of risk. To apply this method, the agency must be persuaded that sufficiently sensitive and reliable means are used to detect these residue amounts. 35/ Although the two situations are identical from a risk standpoint, the agency has not proposed a similar procedure for regulation of indirect food additives. 36/

Regardless of whether acrylonitrile poses a safety hazard when used in beverage containers, there is no assurance that beverage containers made from other materials are safer or more beneficial. The current law does not permit FDA to compare the risks (or risks and benefits) among all possible containers, or indeed, among direct additives. The law now requires manufacturers to demonstrate safety only of food additives as defined in the statute; the safety of GRAS or prior sanctioned substances used in manufacture need not be proved, so that there is no legal need to show that glass bottles, for example, are safe under Section 409.

Pesticide Residues The Environmental Protection Agency (EPA) registers pesticides and establishes tolerances for pesticide residues in food. FDA enforces these tolerances, established under the authority of Section 408 of the Act. 37/ The pesticide situation presents problems of unintended use or consumption resulting from pesticide drift, other forms of physical migration, misuse, and other aspects of environmental contamination. The application of Sections 408 and 409 to pesticides is discussed in Appendix B, pages 64-70. 38/

New Animal Drugs These substances, residues of which may be present in meat, milk, or eggs intended for human consumption, also must obtain premarket approval. Safety in humans and the animal and effectiveness in the animal are criteria for approval. 39/ A statutory provision modeled on the Delaney clause prohibits the use of new animal drugs that are found to induce cancer when ingested or in other appropriate tests, unless the carcinogenic drug does not adversely affect the recipient animal and does not appear as a residue in human food or in edible animal portions after slaughter. 40/ As noted above, FDA uses a risk assessment method in implementing this clause.

Mechanisms for Enforcing Safety Requirements of the Law

FDA enforces food safety requirements under the Federal Food, Drug, and Cosmetic Act principally by three means. First, the agency relies on court enforcement of statutory provisions and regulations. Second, the agency issues regulations implementing statutory provisions. Third, FDA acts informally through written and oral communication to industry.

For adopting certain types of regulations, Section 701 (e)-(g) of the Act specifies formal rulemaking procedures that provide an opportunity for persons adversely affected by a rule to obtain a public trial-like hearing. When reviewing decisions made through formal rulemaking, courts consider the full record and must sustain a decision that is supported by substantial evidence.

Another type of rulemaking procedure used by the agency is so-called "informal" or "notice and comment" rulemaking. This process is used when the Act does not specify a trial type of proceeding. The procedures employed in this type of rulemaking are specified in the Administrative Procedure Act and are the usual process for developing FDA and other agency regulations. There is no requirement for an opportunity for any type of hearing on the regulatory decision.

Formal rulemaking is required in several types of FDA safety regulation, such as establishing tolerances for unavoidable added contaminants and permanent listing of color additives. To illustrate this process, approval of uses for food additives can serve as an example, although the process varies somewhat among categories of substances.

The filing of a petition for approval of a proposed new food additive, or proposed new uses of an approved additive, initiates the process. (If the subject is a proposal to ban or restrict the use of an existing food additive, FDA initiates the process by publishing a proposal). Such petitions must include the details of proposed use of the additive, proposed labeling, relevant data on methods for determining quantities of the additive in food, results of safety testing, and any proposed tolerances.

If FDA intends to disapprove the petition, the proponent of the use of the additive may request a hearing, although this is not usually done. In the hearing, the proponent of the use is required to prove its "safety." This must be demonstrated by a "reasonable certainty," a standard that may be somewhat easier to meet than "beyond a reasonable doubt." FDA is required by law to consider consumption levels of the additive, cumulative effects with other dietary components, and safety factors.

In response to the filing of a petition, FDA publishes in the Federal Register a brief notice of the filing. The supporting data are available for public inspection at the agency. Public comments on the substance can be submitted before a final rule is published. The agency then publishes a regulation.

A hearing also may be required by a party adversely affected by the rule, although this would be unusual. The format for such hearings includes a pre-hearing conference (at which areas of factual disagreement are identified), the filing of written evidence, limited oral testimony, and limited cross-examination.

Any regulation issued by FDA may be subject to judicial review if a court action is brought by a party whose interests were harmed by the regulation. Such a challenge can be based either on the grounds that the regulatory decision did not accord substantively with the law or Constitution or that FDA did not comply with procedural requirements in establishing the regulation.

Problems in Applying the Statute

Even this brief review of food safety law indicates some of the problems that can arise in applying the statute to particular food substances. 41/ These include classification, limits on FDA authority and procedure, and problems in risk assessment.

There are clear difficulties in classifying many substances, and classifications overlap. Nitrites may be prior sanctioned in red meat but not in poultry, and when not prior sanctioned, might be a food additive or a color additive. Mercury in fish may be a natural constituent and/or a contaminant, depending on whether it is concluded to have been "added."

Classification is important in the current state of the law largely because the categories are the basis for application of different statutory standards and procedures. However, the standards are imprecise and involve a range of overlapping and incommensurate terms, such as "unsafe," "poisonous or deleterious," "injurious to health," "ordinarily . . . injurious to health," and "necessary for the protection of public health." In some categories, certain benefit-related factors, such as the "unavoidability" of contaminants and the intended uses of additives, are statutory criteria, whereas for other categories the statute does not require consideration of the benefits of a substance or may prohibit such consideration. Due to the classification-based statutory criteria, benefits tend to be considered only implicitly and inconsistently.

Several criticisms of the statutory classification system can be made. There may be too many categories. The classifications are difficult to understand and have unclear consequences that generally do not bear a discernible relationship to risks. (To illustrate, a substance actually can be banned more easily as a GRAS substance than as a food additive, because procedures required in regulating food additives can be cumbersome.) The classification system also incorporates exceptions based on when the substance attained use.

The classification system serves to focus regulatory attention on certain types of food substances to the neglect of others. Substances defined as food additives must be tested for safety and approved individually. But many food substances remain unregulated. Thus, the classification system inhibits the allocation of regulatory measures proportionate to the degree of risk.

In some ways, the law also appears to limit FDA's regulatory scope and options. FDA's authority to require warning labels on food packages is not explicitly stated in the Act and thus is unclear and relatively untested. The agency lacks authority to restrict food distribution to certain establishments or to certain groups. FDA does not have power to restrict advertising, such as prohibiting advertising directed at risk-susceptible populations or requiring that information on health risks be included in advertisements, although the agency can cooperate with the Federal Trade Commission and can prevent misbranding. The agency has very limited authority in regulating the formulation and labeling of vitamins and minerals as the result of recent restrictions imposed by the Congress. 42/

Some problems may be inherent in any food safety regulatory process. The leading problem may concern the uncertainty of information, for the regulatory agency must make decisions about substances whose risks are poorly understood. Interaction among substances or their effects is a related problem, creating difficulties in ascertaining or limiting the possible health hazards of individual substances through regulation. 43/

Other problems concern implementation of the law. FDA must decide, for instance, whether it should allow blending of an excessively contaminated batch of product with a relatively pure batch to produce a mix that complies with the prevailing tolerance level. Another problem is that formal trial-like regulatory proceedings are cumbersome and time-consuming. To act quickly in the face of elaborate procedural requirements for setting forward tolerance levels, FDA has set so-called "action levels," which can be established with relatively little public participation but are more easily overturned by a court; the law does not provide for "notice-and-comment" rulemaking for tolerances as an intermediate course. Finally, because testing requirements could not be applied immediately to thousands of food substances, those substances approved for use before 1958 have not been subjected to requirements of proof of safety.

Additional regulatory issues emerge from a closer examination of the substances discussed in the next chapter.

REFERENCES AND NOTES

1. P.L. 59-384, 34 Stat. 768 (signed into law by President Theodore Roosevelt June 30, 1906), popularly known as the Wiley or Heyburn Act.

2. P.L. 75-717, 52 Stat. 1040 (signed into law by President Franklin D. Roosevelt June 25, 1938), popularly known as the Copeland Act. See Charles O. Jackson, Food and Drug Legislation in the New Deal (Princeton, N.J.: Princeton University Press, 1970). Officially termed the Federal Food, Drug, and Cosmetic Act, this measure remains the statutory foundation of current law, codified in Title 21 of the U.S. Code.

3. P.L. 85-929, 72 Stat. 1784 (1958).

4. P.L. 86-618, 74 Stat. 396 (1960).

5. P.L. 90-399, 82 Stat. 343 (1968).

6. William Cooper, Program Planning Group Leader, Office of Management, Bureau of Foods, Food and Drug Administration, personal communication, December 21, 1978.

7. Jones v. Rath Packing Co., 430 U.S. 519 (1977); Cosmetic Tioletry and Fragrance Association v. Minnesota, 440 F. Supp. 1216 (D. Minn., 1977), aff'd 575 F.2d 1256 (8th Cir., 1978).

8. Association of Food and Drug Officials, "State Laws and Regulations Profile" (Washington, D.C., mimeographed, 1978).

9. Ibid.

10. Ibid.

11. The lower state limit on polybrominated biphenyls stems from claims of Michigan farmers on chemical and insurance companies following infestation of livestock there in 1974. The limit was authorized against the recommendations of federal and state scientists. Kenneth Van Patten, Assistant Deputy Director, PBB Action Unit, Michigan State Department of Agriculture, personal communication, November 8, 1978.

12. This action was established following incidents of widespread aflatoxin contamination in cottonseed in the 1978 harvest. The economic interest of producers and of the state economy in general are given as reasons fo. the higher 100 ppb tolerance established following a reportedly extensive health risk assessment by Arizona

officials. J.H. Paulson, Deputy Administrator, Office of the Arizona State Chemist, personal communication, November 8, 1978. The higher tolerance also was based on an FDA interim measure taken in 1977. FDA considers Arizona's level unjustifiably high. Taylor Quinn, Associate Director of Compliance, Bureau of Foods, Food and Drug Administration, personal communication, December 21, 1978.

13. Association of Food and Drug Officials, supra note 8. FDA lacks such embargo authority.

14. Food and Drug Administration, "State Programs and Services in Food and Drug Control," by Richard A. Moats (Rockville, Maryland: September 1978, mimeographed), p. 19.

15. Richard A. Merrill, Appendix B of this report.

16. Section 402 (a) (1) of the Food, Drug and Cosmetic Act (hereafter referred to as the Act), 21 U.S.C. Sec. 342 (a)(1), provides:

> A food shall be deemed to be adulterated —
>
> (a)(1) If it bears or contains any poisonous or deleterious substance which may render it injurious to health; but in case the substance is not an added substance such food shall not be considered adulterated under this clause if the quantity of such substance in such food does not ordinarily render it injurious to health...

17. Section 406 of the Act, 21 U.S.C. Sec. 346, provides:

> Any poisonous or deleterious substance added to any food, except where such substance is required in the production thereof or cannot be avoided by good manufacturing practice shall be deemed to be unsafe for purposes of the application of clause (2) (A) of section 402(a); but when such substance is so required or cannot be so avoided, the Secretary shall promulgate regulations limiting the quantity therein or thereon to such extent as he finds necessary for the protection of public health, and any quantity exceeding the limits so fixed shall also be deemed to be unsafe for purposes of the application of clause (2)(A) of section 402(a) .... In determining the quantity of such added substance to be tolerated in or on different articles of food the Secretary shall take into account the extent to which the use of such

> substance is required or cannot be avoided in the production of each such article, and the other ways in which the consumer may be affected by the same or other poisonous or deleterious substances.

Some added contaminants may be avoidable. Under Sections 402(a)(2)(A) and 406, a food containing any added poisonous or added deleterious substance is considered adulterated and unsafe, unless its use is permitted as an unavoidable added contaminant, food or color additive, pesticide residue, or new animal drug.

18. 21 C.F.R. 109.3(c), (d), 42 Fed. Reg. 52814, 52815, 52819 (September 30, 1977).

19. See, e.g., United States v. An Article of Food Consisting of Cartons of Swordfish, 395 F. Supp. 1184 (S.D.N.Y., 1975); United States v. 1200 Cans, Pasteurized Whole Eggs, 393 F. Supp. 131 (N.D. Ga., 1972); United States v. 1232 Cases of American Beauty Brand Oysters, 43 F. Supp. 749 (W.D. Mo., 1942); United States v. Anderson Seafoods, Inc., 447 F. Supp. 1151 (N.D. Fla., 1978).

20. See Appendix B, pp. 32-34.

21. Section 201 (s) of the Act, 21 U.S.C. Sec. 321 (s), provides that for purposes of the Act:

> The term "food additive" means any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food; and including any source of radiation intended for any such use), if such substance is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of

> its intended use; except that such term does not include -
>
> (1) a pesticide chemical in or on a raw agricultural commodity; or
>
> (2) a pesticide chemical to the extent that it is intended for use or is used in the production, storage, or transportation of any raw agricultural commodity; or
>
> (3) a color additive; or
>
> (4) any substance used in accordance with a sanction or approval granted prior to the enactment of this paragraph pursuant to this Act, the Poultry Products Inspection Act (21 U.S.C. 451 and the following) or the Meat Inspection Act of March 4, 1907 (34 Stat. 1260), as amended and extended (21 U.S.C. 71 and the following); or
>
> (5) a new animal drug.

22. 21 C.F.R. 171.1. Agency guidelines suggest that at least four and possibly more than ten valid studies must support a petition for approval of a direct food additive. C. Kokoski and H.R.G. Gittes, "Toxicological Testing Under Varying Food and Color Additive Situ tions" (Food and Drug Administration, mimeographed, May 25, 1977), p. 1-2. Required tests include (1) lifetime feeding study — rodent with in utero exposure for carcinogenesis and chronic toxicity; (2) lifetime feeding study — rodent, for carcinogenesis; (3) short term (6 months to 1 year) feeding study — non-rodent; (4) multi-generation reproduction feeding study (3 generation, 2 litters/generation, with teratology phase) — rodent. A teratology study is required if the need is indicated by available data. Required if needed as preliminary to further study are: (1) acute toxicity test — rodent; (2) acute toxicity test — non-rodent; (3) subchronic feeding study (90 day) — rat. Suggested are: (1) mutagenicity screen; (2) metabolism studies. Toxicologic data on humans should be furnished if available. The lifetime studies should be with more than one species.

23. Section 409 (a) provides:

> A food additive shall, with respect to any particular use or intended use of such additive, be deemed to be unsafe for the purposes of the

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> application of clause (2)(C) of section 402 (a), unless
>
> * * *
>
> (2) There is in effect, and it and its use or intended use are in conformity with, a regulation issued under this section prescribing the conditions under which such additive may be safely used.

Paragraph (3) of Section 409 (c) provides:

> No such regulation shall issue if a fair evaluation of the data before the Secretary [of DHEW] -
>
> (A) fails to establish that the proposed use of the food additive, under the conditions of use to be specified in the regulation, will be safe ... (emphasis added).

The emphasized portion may be considered the general safety clause.

For reference, Section 402 (a)(2)(C) referred to in Section 409 (a) specifies that a food is adulterated "if it is, or it bears or contains, any food additive which is unsafe within the meaning of Section 409...."

24. Section 409 (c)(3)(A) of the Act, 21 U.S.C. Sec. 348 (c)(3)(A).

25. FDA in 1977 proposed to ban saccharin from use as a food additive under the Delaney clause and the general safety clause, 42 Fed. Reg. 19996 (April 15, 1977); in P.L. 95-203 (1977), the Congress prohibited the banning of saccharin pending the results of this study. Action under the anticancer provision of Section 512(d)(1)(H), applicable to new animal drugs that leave residues in food or in edible portions of slaughtered animals, is pending with respect to the new animal drugs diethylstilbestrol, (DES), 41 Fed. Reg. 1804 (January 12, 1976), see also 41 Fed. Reg. 52051 (November 2, 1976), notwithstanding the fact that the exemption for drugs that do not leave residues was intended to protect DES and is called the "DES proviso," and nitrofurans, 41 Fed. Reg. 19907 (May 13, 1976). Cyclamates were GRAS and therefore not subject to the Delaney clause when they were banned, 34 Fed. Reg. 17063 (October 21, 1969). Other than these four instances, the Delaney clause was used as authority only in bans against the indirect additives chroanaline, used in food packaging and polyurethane manufacture, 34 Fed. Reg. 19073 (December 2, 1969); Flectol H, a component of packaging adhesives, 32 Fed. Reg. 5675 (April 7, 1967); and chloroform, 41 Fed. Reg. 15029 (April 9, 1976) (pending).

26. See, e.g., Charles H. Blank, "The Delaney Clause: Technical Naivete and Scientific Advocacy in the Formulation of Public Health Policies," 62 California Law Review 1084 (1974), and John C. Kirschman,

"Toxicology - The Exact Use of An Inexact Science," 31 Food-Drug-Cosmetic Law Journal 455 (1976).

When FDA was about to issue its proposal to ban saccharin, Representative James Martin (Republican of North Carolina) and ten co-sponsors introduced a bill that would amend the Delaney clause to require FDA to appoint a broadly based advisory committee to weigh the health risks and "benefit to the general public" of a carcinogenic food additive before acting to ban it. The committee would have been composed of scientists "qualified ... to evaluate the carcinogenic effect of the food additive," consumer and industry representatives, nutritionists, economists, scientists, and lawyers. On deciding whether the risks outweighed the benefits, the committee would have been required to perform six specific tasks, including:

- determining whether tests animals were administered doses out of proportion to expected human consumption levels
- evaluating the quality of test data
- assessing epidemiologic evidence
- evaluating "any known biological mechanism of the carcinogenic effect of the food additive"
- assessing the possibility of reducing human exposure to the risks
- predicting effects of a ban or approval on health risks and benefits, nutrition, the environment, and the public interest generally.

H.R. 5166, 95th Cong., 1st Sess. The bill was not reported out of committee.

27. See, e.g., James S. Turner, "The Delaney Anti-cancer Clause: A Model Environmental Protection Law," 24 Vanderbilt Law Review 889 (1971), ~~and~~ Samuel S. Epstein, "The Delaney Amendment," Preventive Medicine 2: 140-149 (1973).

However, when the Delaney clause was proposed, DHEW's view was that no additive banned under the clause would be considered safe under the general safety clause. This view was contained in a letter to Delaney from then Assistant DHEW Secretary Elliot Richardson. See 104 Cong. Rec. 17414, 17415 (August 13, 1958).

28. Section 409 (c) (5) of the Act, 21 U.S.C. Sec. 348 (c) (5).

29. Section 409 (b)(2)(C) of the Act, 21 U.S.C. Sec. 348 (b)(2)(C), requires that food additive petitions must contain:

> All relevant data bearing on the physical or other technical effect such additive is intended to produce, and the quantity of such additive required to produce such effect.

Section 409 (c)(4) provides:

> If, in the judgment of the Secretary, based upon a fair evaluation of the data before him, a tolerance limitation is required in order to assure that the proposed use of an additive will be safe, the Secretary -
>
> (A) shall not fix such tolerance limitation at a level higher than he finds to be reasonably required to accomplish the physical or other technical effect for which such additive is intended;
>
> (B) shall not establish a regulation for such proposed use if he finds upon a fair evaluation of the data before him that such data do not establish that such use would accomplish the intended physical or other technical effect.

30. 21 C.F.R. 182, 184.

31. Section 706 of the Act, 21 U.S.C. Sec. 376, governs regulation of color additives in foods, drugs, and cosmetics. The anti-cancer provision is contained in sub-paragraph (b)(5)(B) of the section and provides:

> A color additive (i) shall be deemed unsafe, and shall not be listed, for any use which will or may result in ingestion of all or part of such additive, if the additive is found by the Secretary to induce cancer when ingested by man or animal; or if it is found by the Secretary, after tests which are appropriate for the evaluation of the safety of additives for use in food, to induce cancer in man or animal, and (ii) shall be deemed unsafe, and shall not be listed, for any use which will not result in ingestion of any part of such additive, if, after tests which are appropriate for the evaluation of the safety of additives for such use, or after other relevant exposure of man or animal to such additive, it is found by the Secretary to induce cancer in man or animal.

32. See supra note 21.

33. 42 Fed. Reg. 48528, 48529 (September 23, 1977).

34. 41 Fed. Reg. 23940 (June 14, 1976), 21 C.F.R. 121.4010.

35. FDA has adopted a modified Mantel-Bryan method of assessing human cancer risks from new animal drugs on the basis of a dose-response curve. 42 Fed. Reg. 10412 (February 22, 1977): See also Appendix F.

36. It is not clear whether the law would permit application of a risk assessment procedure to indirect additives. Unlike the Delaney clause that applies to direct and indirect food additives, the anti-cancer provision applicable to new animal drugs authorizes FDA to establish procedures for detecting residues (in edible animal portions after slaughter and in food yielded by or derived from living animals). Sec. 512(d)(1)(H) of the Act, 21 U.S.C. Sec. 360b (d)(1)(H). Another reason for not applying risk assessment procedures to acrylonitrile is the lack of animal test data, 42 Fed. Reg. 48528, 48538 (September 23, 1977).

37. Section 408(b) of the Act, 21 U.S.C. Sec. 346a(b), provides in part:

> (b) The Secretary shall promulgate regulations establishing tolerances with respect to the use in or on raw agricultural commodities of poisonous or deleterious pesticide chemicals and of pesticide chemicals which are not generally recognized, among experts qualified by scientific training and experience to evaluate the safety of pesticide chemicals, as safe for use, to the extent necessary to protect the public health. In establishing any such regulation, the Secretary shall give appropriate consideration, among other relevant factors, (1) to the necessity for the production of an adequate, wholesome, and economical food supply; (2) to the other ways in which the consumer may be affected by the same pesticide chemical or by other related substances that are poisonous or deleterious; and (3) to the opinion of the Secretary of Agriculture. * * * In carrying out the provisions of this section relating to the establishment of tolerances, the Secretary may establish the tolerance applicable with respect to the use of any pesticide chemical in or on any raw agricultural commodity at zero level if the scientific data before the Secretary does not justify the establishment of a greater tolerance.

38. In registering pesticides, EPA considers economic, social, and environmental benefits. See Sections 2(bb), 3(c)(5), 6 (b) of the Federal Insecticide, Fungicide, and Rodenticide Act (P.L. 94-140) as amended, 7 U.S.C. Secs. 136 (bb), 136d (b).

39. Under Sec. 512(d)(1)(E), a new animal drug must be banned by the DHEW Secretary if

> evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof.

Under Sec. 512(d)(3), the term "substantial evidence" as used in Sec. 512(d)(1)(E) means

> ...evidence consisting of adequate and well-controlled investigations, including field investigation, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and reasonably be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

40. Section 512(d)(1)(H) of the Act, 21 U.S.C. Sec. 360b (d)(1)(H). One court has declared as dicta that, notwithstanding the anti-cancer provision of Section 512, FDA must approve animal drugs if the benefits outweigh the risks, Hess and Clark, Div. of Rhodia, Inc. v. FDA, 495 F. 2d 976, 993-994 (D.C. Cir., 1974).

41. For a discussion of current problems in food safety regulation under the Act, see especially Peter Barton Hutt, "The Basis and Purpose of Government Regulation of Adulteration and Misbranding of Food," 33 Food-Drug-Cosmetic Law Journal 505 (1978).

42. P.L. 94-278 (1976), Section 411 of the Act, 21 U.S.C. Sec. 350.

43. To illustrate, certain calcium and phosphorous compounds individually might normally be considered safe, whereas disruption of the calcium-phosphorous balance could prove toxic. R.G.H. Siu, et al., "Evaluation of Health Aspects of GRAS Food Ingredients: Lessons Learned and Question Unanswered," Federation Proceedings of the Federation of American Societies for Experimental Biology (1977), pp. 2519-2562, see pp. 2549-2550.

Chapter 3

ISSUES IN FOOD SAFETY REGULATION: FOUR ILLUSTRATIVE CASES

This chapter summarizes four cases that illustrate a range of topics and problems in food safety. The examples are saccharin, mercury, nitrite, and aflatoxin. These cases provide concrete examples of the issues and policy options to be discussed in later chapters.

The technical assessment of saccharin risks and benefits was developed from Part 1* of this report. The other three cases have not been analyzed as comprehensively as saccharin, although experts for each of the three other cases compiled and reviewed the material presented here.

The information for each case illustration is presented under the general headings of background, risks, benefits, regulatory considerations, and issues.

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*Assembly of Life Sciences and the Institute of Medicine, Committee for a Study on Saccharin and Food Safety Policy, Saccharin: Technical Assessment of Risks and Benefits. Washington, D.C.: National Academy of Sciences, 1978. The saccharin report was primarily the responsibility of Panel 1 and the Committee.

CASE ILLUSTRATION: SACCHARIN*

Saccharin** was selected as a case illustration because of current controversy over it and because, as a non-nutritive sweetener, it is a direct additive for which there is at present no approved substitute. It poses a carcinogenic risk of uncertain dimension to humans but, as a non-nutritive sweetener, also yields perceived benefits for certain subpopulations.

Background

For more than 70 years saccharin has been used as a substitute for sugar in the United States. For almost that same length of time its safety has been the subject of scientific and regulatory controversy.

Over the last quarter century, a number of factors have combined to focus attention on the potential risks of saccharin use and to raise the question whether it should be removed from use as a food additive. In addition to factors that are directly related to saccharin use, there are other factors that affect the climate of opinion in which a decision will be made on the availability of saccharin.

Consumption Data

Incompletely analyzed data on consumption patterns of saccharin are presented in Part 1 of this report. The Committee does not wish to draw definitive conclusions from the data, but directs attention to apparent trends:

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*See Chapter 10 for saccharin regulatory options.

**See Saccharin: Technical Assessment of Risks and Benefits for greater detail. The study on saccharin was primarily the responsibility of Panel 1 and the Committee.

- The percentage of the population consuming saccharin-containing foods and the amounts consumed are increasing. The percentage of young children that consume saccharin is also rising. Young children consume fewer total milligrams per user than do adults, but the amount per unit of body weight often surpasses the intake among adults, as would be the case with any food components. A major problem remains in interpreting these data: does the increase in saccharin consumption add to or replace sugar or other calorie consumption? The consideration of both risks and benefits will be influenced by the answer to this question. The committee recommends that further research be performed on consumption patterns.
- Although the percentage of women consuming saccharin was once considerably higher than the percentage of men, the margin of difference between the sexes has narrowed.
- Data indicate that among the greatest users of saccharin are women in the child-bearing years (20 to 39 year age group) and the largest increase in use over the past several years has been in boys from birth to 9 years of age.
- Sixty to 90 percent of all diabetics (or those who classify themselves as diabetics) use saccharin extensively. A greater proportion of dieters (on low-calorie, low-cholesterol, low fat, and other diets) consume saccharin than do non-dieters.
- Soft drinks are the most frequently consumed saccharin-containing products on the market. They account for approximately

90 percent of the recent increased consumption of the sweetener.

Risk Assessment of Saccharin and Its Impurities

Laboratory Investigations

On the basis of the evaluation of the data from laboratory investigations of saccharin, the committee has reached the following conclusions about the toxicity and potential human risks from exposure to saccharin.

(1) Saccharin seems not to be metabolized to any great extent in laboratory animals and its metabolism has not been observed in humans. Because of the limits of experimental detection, it is possible that a small percentage of saccharin may be modified enzymatically. Saccharin is rapidly absorbed via the gastrointestinal tract, is distributed widely throughout the body, crosses the placenta, and is eliminated mainly in the urine. Accumulations of saccharin in several tissues including the bladder have been demonstrated following repeated exposures.

The committee concludes that either saccharin is unusual in that its carcinogenic effects are due to the unmetabolized parent compound or the effects are due to small quantities of undetected metabolites.* The accumulation of saccharin in the bladder epithelium may play a role in the formation of bladder cancer.

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*Although no evidence has been found that metabolism and excretion of saccharin is altered after chronic exposure in animals or humans, the possibility of production of small amounts of carcinogenic metabolites by intestinal microbes adapted to saccharin remains.

(2) When tested in two-generation studies, saccharin is a bladder carcinogen for male rats. A significant increase in bladder cancer was found consistently in male offspring exposed continuously in utero and throughout life. In one two-generation study, a significant increase in bladder cancer occurred in males of the parental generation. Studies using saccharin in combination with some chemical carcinogens have shown that saccharin promotes tumor development in the bladder of rats. Because humans are exposed to a variety of chemical carcinogens in their environment, the carcinogenic risk from saccharin as a promoter may be considerably greater than that indicated by the single compound studies. Because the process of cancer promotion is little understood, the estimation from these experimental data of risks to humans is not feasible at present.

The committee concludes that the interpretation of the results of the two-generation chronic studies was not artificially influenced by the following factors in design: the doses studied (maximum tolerated dose); in utero exposure; high sodium content of diet in treated as opposed to control animals; and the possibility of microcalculi in the urinary bladder of treated as opposed to control animals. Because animal studies that are properly conducted to detect carcinogenic activity are qualitatively predictive of human responses, the committee concludes that saccharin ingestion poses a potential cancer risk to humans. However, because of the substantial uncertainties in extrapolating from experimental animal doses to human exposure levels, the committee concludes that quantitation of risk to humans cannot be made with confidence at present.

(3) An increase in benign uterine tumors and ovarian lesions in saccharin-treated rats was suggested in a few studies.

(4) Orthotoluenesulfonamide (OTS), the major impurity of the saccharin manufactured through the Remsen-Fahlberg (RF) process, was not found to be carcinogenic in rats in a study properly designed to detect carcinogenesis. The possibility that other minor impurities of saccharin are responsible for carcinogenic activity of commercial saccharin cannot be eliminated. However, the committee believes that the probability of occurrence is extremely remote for the following reasons: (a) RF saccharin used in animal studies by the Food and Drug Administration and the Wisconsin Alumni Research Foundation had different patterns of impurities, yet produced the same carcinogenic responses (i.e., bladder cancer in males); (b) more purified saccharin manufactured through the Maumee process has also produced bladder cancer in males; (c) in Maumee saccharin, the impurities are present in such low concentrations that to be carcinogenic, they would have to be enormously potent.

(5) Short-term tests for genetic rather than directly registered carcinogenic effects have been conducted with saccharin and

some of its impurities. Results of 16 assays were negative, while those of five (including a promotion assay) were positive. Because these assays evaluate varying types of genetic effects and because saccharin appears to be a carcinogen of low potency (requiring high dosage), the variation in findings might be expected. The committee concludes that interpretation of these studies is compatible with that of the in vivo carcinogenic effects; however, the results do not provide definitive information for estimating risks to humans.

Human Studies

The committee reviewed the epidemiologic studies of the relationship between saccharin and bladder cancer and between saccharin and spontaneous abortion. With one exception, findings indicated the absence of a health hazard for either sex. However, there were many methodological deficiencies in the negative studies.

(1) Time-trend studies by Armstrong and Doll in 1974 1/ and by Burbank and Fraumeni in 1970 2/ provide no evidence that saccharin use is necessarily associated with cancer. The method however, may be too insensitive to separate the effects of saccharin from known bladder cancer risk factors, such as cigarette smoking.

(2) Studies on diabetics, by Armstrong et al. in 1976, 3/ by Armstrong and Doll in 1975 4/, and by Kessler in 1970, 5/ do not show a positive association between saccharin use and bladder cancer, but these studies have limitations that

hinder assessment of the risk of saccharin: (a) findings in diabetics may not be equally applicable to a non-diabetics; (b) individual saccharin consumption was not measured; and (c) there were no data on smoking habits and the representation in the sample of certain occupations that are known to be associated with bladder cancer.

(3) Case-control studies do not provide clear evidence to support or refute an association between saccharin use and bladder cancer. Two studies of sufficient size for reliable measurement of low-level effects of saccharin were conducted by Howe et al. in 1977 6/ and by Kessler and Clark in 1978. 7/ The study by Howe et al. used a complex method to estimate the relative risk of bladder cancer in users and non-users of non-nutritive sweeteners. This study reported that the proportion of male bladder cancer patients who used non-nutritive sweeteners is significantly higher (risk ratio of 1.6) than the proportion of male controls. The study by Kessler and Clark reported no statistically significant excess risk for either sex, and is thus consistent with no excess cases of bladder cancer attributed to the use of saccharin. The committee believes that there are methodologic limitations of each study that do not allow a choice between the seemingly contradictory results. Four other case-control studies—those by Kessler in 1976, 8/ Morgan and Jain in 1974, 9/ Wynder and Goldsmith

in 1977, 10/ and Simon et al. in 1975 11/--have not demonstrated a statistically significant risk, but these studies have major deficiencies that severely limit the conclusions that can be vigorously drawn.

The committee suggests two additional epidemiologic approaches that might be used to assess the risk of saccharin: 1) data from prospective studies in which accurate dietary information had been collected; and 2) surveys to assess the risk of bladder cancer in workers (a small number) who are involved in the production and handling of saccharin. These workers might be compared, both retrospectively and prospectively, with those employed in other areas of the same plant.

Assessment of Benefits*

Data on the efficacy of saccharin in dietary management of health problems are sparse. It is not possible either to dismiss or accept the claims of benefits that have been made, and there is no scientific evidence to show objective and direct benefits to health from saccharin.

Human beings appear to have a marked predilection for sweet foods. The committee recognizes therefore, that there is a perceived need and perhaps even psychological reliance on non-nutritive sweeteners by certain segments of the population. The overall significance of this potential psychologic motivation has not been evaluated as to benefit beyond satisfaction of the motivation itself.

Concerning the benefits to physical health:

(1) Scientific evidence does not permit assessment of the role that saccharin plays in weight control or dietary compliance,

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*See Chapter 6 for a general discussion for assessing benefits.

though these are both key factors in the prevention or treatment of obesity and diabetes. Five studies on management of obesity with non-nutritive sweeteners and three studies pertaining to diabetes were reviewed by the committee. The design of the studies were considered to be inappropriate for assessing the efficacy of saccharin in weight control or diabetic management.

(2) Information on the efficacy of saccharin in general health maintenance is sparse and in many cases inadequate.

(3) Long-term, well-controlled clinical trials using saccharin specifically to control obesity or diabetes have not been performed. It is in fact, uncertain that a satisfactory study can be conducted to answer the necessary questions directly. The committee suggests nonetheless, that attempts at this type of study should continue and that short-term, retrospective, and other limited studies should be pursued to provide indirect estimates of benefits.

(4) The long-term consequences to diabetics of increased reliance on nutritive sweeteners have not been examined adequately.

(5) A recent review by the Federation of American Societies for Experimental Biology 12/ does not support the opinion that most dietetic foods are a necessity for the diabetic diet. However, despite the lack of objective evidence of efficacy of non-nutritive sweeteners in the dietary management of chronic disease or the maintenance of weight in the normal individual, some attention must be given to the preponderance

of practitioner opinion that favors the use of non-nutritive sweeteners in weight reduction or treatment of diabetes.

(6) The data are not conclusive as to whether saccharin may have potential as a non-carciogenic substitute for sugar. It may have a bacteriostatic effect and may lead to reduced plaque formation in the short term, but its non-cariogenic effect has not been studied clinically.

(7) There are probable benefits in making more palatable dentifrices and therapeutic drugs in order to promote their proper use.

(8) Substitution of sugar for saccharin in snack foods and possibly in soft drinks, should it occur, can be expected to lead to an increased incidence of dental caries.

(9) There are varying estimates and only limited data to indicate the extent to which sugar would be substituted for saccharin, should saccharin become unavailable. From 1969 to 1970, there was a decrease in the per capita use of non-nutritive sweeteners following the ban on cyclamates. This was not accompanied by a measurable increase in the use of nutritive sweeteners. In addition, the association of increased sugar consumption with obesity or related health problems is unclear.

Regarding psychological implications:

(1) Available evidence does not indicate what proportion, if any, of the human desire for sweets is an innate biological need

and what is an acquired preference resulting from cultural exposure.

(2) Public opinion polls suggest a perceived need or psychological reliance on non-nutritive sweeteners by certain segments of the population. Therefore, if saccharin were removed from the market, a significant segment of the population may experience psychological stress of a transient or long-term nature. Some special groups, such as juvenile diabetics, may be particularly affected if low-calorie foods and beverages, which enable a more normal way of life, are removed without suitable replacement.

Regulatory Considerations

The first federally initiated study on the safety of saccharin was undertaken in 1911, and saccharin has been a subject of regulatory controversy almost since enactment of the original Food and Drug Act of 1906. After enactment of the Food Additives Amendment of 1958, FDA treated saccharin as a GRAS substance until 1972. Its removal from the GRAS list that year reflected FDA's concern over increased saccharin consumption and perceptions of a possible cancer risk. Upon removing saccharin from its GRAS list, FDA issued interim regulations permitting certain uses of the substance, including use as a non-nutritive tabletop and soft drink sweetener, pending further study. 13/

On April 15, 1977, following release of the results of a Canadian study on rats, FDA proposed to revoke the interim regulations and prohibit the use of saccharin as a food additive. 14/ The Federal Register notice announcing the proposal stated that the agency would consider new drug applications for approval of saccharin as a single-ingredient over-the-counter drug. Many constituent letters to members of Congress and other adverse criticism of the proposal encouraged Congress to forestall implementation of the proposed ban. On November 23, 1977, the Saccharin Study and Labeling Act became law, prohibiting a ban pending completion of this study and establishing labeling requirements for the interim period. 15/

Classification and Jurisdiction

Assuming that saccharin is neither a drug nor GRAS, saccharin used in packaged foods and as a tabletop sweetener is a food additive under the Federal Food, Drug and Cosmetic Act. It therefore is subject to Section 409 of the Act, which prohibits any use of a food additive not approved by FDA and authorizes FDA to approve the use of an additive only if it is "safe." The 1977 proposed ban was based both on the general safety clause of Section 409 and on the Delaney clause, which specifically prohibits approval of any food additive found in appropriate tests to induce cancer in humans or animals.

Issues

1. The saccharin case highlights an important current issue in the science of food safety evaluation—the testing, evaluation and regulation of cancer promoters. Current knowledge indicates that 1) cancer promoters may not themselves be mutagenic or genotoxic, and 2) whatever may be the case for carcinogens, there may be a threshold for the promotion effect. Thus, emerging evidence of saccharin as a promoter of cancer raises issues that are of major consequence with regard to regulatory

mechanisms for substances that pose cancer risk. For example, what is the appropriate regulatory mechanism for handling compounds that facilitate cancer development yet alone do not induce cancer? Does the Delaney clause, which prohibits FDA from approving additives that "induce" cancer, thereby prohibit FDA from approving cancer promoters? In addition, saccharin strongly emphasizes the need for a much more versatile regulatory approach to management of suspected or demonstrated promoting agents.

2. Saccharin also emphasizes the problem of special populations for regulatory processes. People concerned with weight control, diabetics, and children consume large amounts of saccharin compared with other segments of the population; and some groups, such as children and men, appear to be at higher risk than others.
   The distribution of risks and benefits among subpopulations raises regulatory issues that the current law does not appear to contemplate. The law does not authorize FDA to determine safety for different population groups, nor does it specifically authorize regulatory measures, such as targeted information dissemination or restricted distribution, involving people at especially high risk. Substantial, practical difficulties would attend regulatory efforts to effectively reduce consumption for certain subpopulations.
3. The long duration of the saccharin controversy indicates that the actual health risks of a particular food substance are not easily ascertained. Safety decisions, even after considerable study as in the case of saccharin, involve enough scientific uncertainty to confound efforts to assign a numerical or ordinal value to the risk posed by a food

substance. Additionally, in saccharin and other cases, the regulatory determination of safety is complicated by the question of how to interpret data that are not subject to the rigorous peer review characteristic of the scientific process.

4. Although it has limited resources, FDA is responsible for assuring the safety of the nation's entire food supply. Ideally, one would expect that limited resources would be allocated according to anticipated level of risks, with the agency assigning its highest priority to substances that may pose the most serious damage to health. Through the years, saccharin has commanded much time and resources of investigators, advisory committees, regulators, and government officials. Some may argue that available evidence concerning the risk of this substance is not at the moment commensurate with the concentrated attention it has received. However, the recent involvement by the Congress in the saccharin controversy may have served as a stimulus for congressional review of food safety regulation. In this sense, the considerable attention and resources devoted to the saccharin problem may prove to have been useful and appropriate.

5. Saccharin highlights the problem of considering health and non-health benefits when regulating food safety. Current law, which presents a simple dichotomy of "safe" and not proved to be "safe" as a criterion for the approval of food additives, makes no allowance for the possibility that health benefits might offset health risks.

   Estimation of net saccharin advantages also involves the fact that there is no other legally permitted non-nutritive sweetener.* There is the additional question of whether saccharin's perceived benefits should be considered more fully because of the substance's long history of use. Clearly, if benefits are to play a formal role in the regulatory process, then benefits must be studied under equivalent quality terms with investigations of risks.

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*See Chapter 4 for a discussion of the decision-making process with regard to approval of a safer substitute.

6. The continuing saccharin controversy is widely perceived in the context of the Delaney clause. Although FDA asserts that saccharin should be banned under the general safety clause as well as the Delaney clause, some aspects of the implementation of the Delaney clause relative to saccharin raise important questions.

   First, the Delaney clause, like the general safety clause which it qualifies, strongly implies that the applicable federal policy goal, as illustrated by cancer, is zero risk of harm from food additives. The general criterion of "safety" substantiates this implication. But the lack of scientific plausibility in the notion of zero risk in any class of compounds raises the question of more feasible goals, taking into account feasibility in a free society, as well as securing for the society the maximum public health benefit.

   Second, the Delaney clause treats cancer differently from other diseases in safety legislation. Under the clause, it is difficult to avoid focusing scientific and regulatory attention on cancer.

   In general, the Delaney clause and the general safety clause represent statutory specification and rigidity. Included are lack of acknowledgement of benefits, whether health, or non-health, non-acceptance of the reality that nothing is absolutely safe, and lack of a mechanism for adjusting the regulatory process to developments in testing technology, to new findings about previously unanticipated health risks, and to new approaches for targeting safety regulation to the population groups at greatest risk. The Delaney clause specifically excludes, for additives found to induce cancer in humans or laboratory animals, intermediate regulatory measures, such as tolerance levels, warning labels, or restrictions on use.

Thus, while embodying many features that make it a less than typical case as a regulatory prototype, saccharin highlights the problems of sharply defined and rigidly peremptory regulatory statute in a complex area such as food safety.

CASE ILLUSTRATION: MERCURY

Mercury, in the form of methylmercury, is a naturally-occuring toxic substance found in certain foods, such as fish, that are consumed by human beings. It also accumulates to high levels in areas of industrial mercury processing. Therefore, it can be considered both as a contaminant and as a natural constituent of food. Mercury in food has no benefit in itself but many of the foods that contain mercury are desired items in the diet and also provide nutritional benefit.

Background

Mercury is a chemical element with unusual properties. It is among the heaviest elements, yet it is liquid at normal room temperature and quite volatile. It is a good electrical conductor, it has high density and surface tension and it readily forms alloys with other metals. It is a stable element that does not decompose readily and therefore is not easily disposed of. Its chemical properties allow it to combine with other elements to form both organic and inorganic molecules.

Mercury is not among the most abundant metals but it is widely distributed in the earth's crust, mostly in the form of concentrated ores. The element and its compounds are also widely disseminated in a natural global cycle. The major sources of mercury in this cycle are natural degassing of the earth's crust and deposition of mercury from the atmosphere. As a result of the common technological use of mercury and its compounds, human activities are estimated to contribute 25-30% of the total atmospheric mercury burden. 1/

Special Features of Mercury as a Hazardous Food Constituent

Mercury is a normal, low level constituent of living organisms but serves no known biological function. In sufficient quantity within the human body the mercury compound methylmercury is a dangerous toxin, damaging particularly the nervous system.

When mercury is used industrially without suitable containment, the concentration of the element and its chemical compounds increases in the local environment surrounding the industrial sites. Serious outbreaks of mercury poisoning have occurred in several instance following human ingestion of foods that have a high methylmercury content derived from environmental sources. 2/

Mercury tends to be concentrated in potent biological compounds as it moves through certain food chains. Mercury is converted by biological reactions to methylmercury, a compound that is more soluble and toxic than the unchanged element. 2/ Particularly in the case of fish, the content of methylmercury may become high enough in the edible flesh to harm human populations that consume considerable quantities of the contaminated fish. The levels of mercury measured in freshwater predatory fish such as bass and pike range from .4 to 1.0 ppm. 1/

Assessment of Risks*

The Nature of the Risk

The health risks of mercury stem from the ready diffusion of methylmercury into cells. Heavy metals (another example is lead) interfere with normal cellular metabolic processes in a number of ways. Mercury, in the form of methylmercury, can cross both the blood-brain barrier and the placenta to accumulate in nerve tissues of either adults or fetuses. Because of its long biological half-life and metabolic stability, mercury gradually accumulates in the central nervous system and induces degenerative changes by unknown mechanisms. 1/

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*See Chapter 5 for a general discussion on concepts for assessing risks.

Chief effects are seen clinically as nervous system disorders. In acute situations these involve paraesthesia (numbness and tingling of the hands, lips, mouth, and feet) followed, with increasing severity, by speech defects, muscular uncoordination, restriction and blurring of vision, blindness, deafness, and ultimately death. In chronic cases, changes of less dramatic and less well-defined nature may occur. There is evidence for effects on cell division during both mitosis and meiosis as well as on fertility in animals. Evidence of mutagenic effects is sparse and conflicting. Teratogenic effects have been observed in laboratory animals and there is clear-cut epidemiologic evidence for brain damage to human fetuses borne by pregnant mothers exposed to methylmercury levels that produced no serious effects in the mothers. 3/ Although data are minimal there is no evidence that mercury acts as a carcinogen.

Evidence of the Risk of Mercury in Food

Under particular conditions, methylmercury in foods can reach levels high enough to cause widespread illness and disease. Such poisoning occurred in Japan in the 1950s from ingestion of contaminated fish, and in Iraq in the early 1970s from fungicide on seed grain. Local waters neighboring or draining from mercury-producing industrial sites show heightened mercury levels, which in turn lead to increased levels of methylmercury in the tissues of fish, shellfish and other aquatic species. Moreover, significantly elevated levels of mercury are found in predatory ocean fish at great distance from the presumed source-sites, although there is no evidence of significantly elevated mercury levels in the ocean waters. The oceans constitute a vast mercury sink whose mercury concentration probably is little affected by human activities. Mercury concentrations in predatory marine fish, therefore, probably have been stable for a long time. 1/

The movement of mercury among atmosphere, land, natural waters, and food chains is not completely understood. Mercury from concentrated sources, such as industrial sites, moves outward in complex patterns that are not now fully predictable. An important element in the distribution chain is the atmospheric mercury burden which comes as a vapor from industrial processing and use of mercury.

As a component of these distribution patterns mercury tends to concentrate in its biologically more dangerous form (methylmercury) in many species, particularly those high in various food chains. However, high mercury content can occur in human foods in other ways. The outbreak in Iraq, the largest instance of methylmercury poisoning ever recorded, was the result of consumption of home-made bread prepared from seed wheat treated with a methylmercury fungicide. 4/ Thus, particular foods may have various levels of mercury contamination, depending upon exposure to varying mercury loads in the environment.

The hazard to particular individuals or subpopulations depends upon the aggregate methylmercury content of the various foods they consume and upon individual or subpopulational sensitivity. At present, methylmercury in food appears to pose a moderate risk to the general U.S. population. However, there may be subsets of the U.S. population, such as those who consume heavily contaminated freshwater fish, that may be at higher than average risk. In rare instances, such as the outbreaks in Japan and Iraq, the concentration of methylmercury in some foods may be sufficient to create a severe public health problem. More generally, the risk levels depend upon consumption of various foods containing different methylmercury levels.

Dietary patterns vary widely in different geographic areas and in different cultural subpopulations, leading to wide variation in risk. For example, in Canada elevated levels of methylmercury in fish from a number of lakes were discovered in 1969. 2/ Some of the lakes were near industrial sites, while others had no obvious source of direct contamination. Human populations in the contaminated area showed greatly differing mercury levels in their blood. The highest levels have been alleged to occur among adult male guides at fishing camps. Their wives also are alleged to have had higher levels than other women in the general area. Thirty-seven of 89 people examined in the contaminated area had signs and symptoms of methylmercury poisoning. These allegations are still subject to scientific corroboration and studies are continuing.

In addition to acute effects of methylmercury poisoning, some evidence suggests that relatively low levels may be potent enough to exert general chronic effects of unknown seriousness. In particular, subpopulations who are at special risk (e.g., fetuses, infants, or persons weakened by other diseases) may undergo unrecognized pathologic processes. 5/ Moreover, subclinical effects of methylmercury poisoning could combine with other factors to contribute, for example, to such conditions of complex etiology as mental retardation. 4/ These situations thus suggest the difficulties of assessing general mercury hazard when there is likely to be high variability of exposure due to food habits, as well as high variability of methylmercury content in food sources.

Assessment of Benefits*

The unintended presence of increased methylmercury in certain foods affords no benefit to consumers of the foods, although the foods themselves are otherwise nutritious and desired items in the diet. For example, fish is an excellent source of high quality protein, with relatively few calories per gram and low in fat.

Benefits that can be ascribed to mercury come from its use as an industrial chemical. Because of its unique properties, mercury is mined, smelted, and widely used in a multitude of industrial processes such as chlorine production in the chlor-alkali industry, electrical conductivity in lamps, arc rectifiers, mercury battery cells and electrical switches, indicator material in thermometers, barometers, and temperature-recording devices, fungicides and pesticides in a variety of applications such as seed coating on grains to retard spoilage, pharmaceuticals and cosmetics, catalysts in various chemical syntheses, and in forming amalgams with gold and silver in dentistry. 6/

For industrial and agricultural use mercury is deliberately concentrated and rendered more available by disassociation from natural ores. Following use it often is released as a by-product to the environment, where it may be methylated both biogenically and abiogenically. Although a substantial curtailment of mercury use would lead to severe economic repercussions in many industries, if industrially-emitted mercury were totally recycled rather than released, essentially all its benefits would be achieved without additional hazard to the food supply.

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*See Chapter 6 for a general discussion on concepts for assessing benefits.

Regulatory Considerations

Regulation of mercury in fish in the U.S. is relatively recent, originating in 1970 with the discovery of mercury in edible fish from the Great Lakes. 7/ The Canadian government that year warned of mercury levels as high as 5 ppm in Great Lakes fish and banned the sale of fish from Lake St. Clair. United States Senate hearings, also conducted in 1970, suggested that the problem affected fish in waters all over this country and that interagency fragmentation of responsibility hindered an appropriate resolution. 8/

In 1974, FDA classified mercury in fish as an unavoidable added contaminant and set an interim action level of 0.5 ppm. 9/ The action level was set pending further study that could clarify the health risks at different levels of contamination. That level remained in effect until 1978, when a federal district court concluded that up to 1.0 ppm mercury in fish was sufficiently safe. 10/ As a result of this decision, FDA has raised its action level to 1.0 ppm, 11/ although the court's interpretation of the statutory provision is on appeal. The action level affects mercury in general, although methylmercury is recognized as the toxic agent.

Classification and Jurisdiction

There are two possible classifications of mercury in fish under the classification scheme used in this report to interpret provisions of the Federal Food, Drug, and Cosmetic Act. First, as FDA maintains, mercury could be an unavoidable added contaminant subject to the agency's tolerance-setting powers under Section 406. This classification is valid, if for purposes of the Act, mercury is a "poisonous or deleterious substance added to [the fish]" and if, in the language of Section 406, mercury in fish "cannot be avoided by good manufacturing practice." Alternatively, mercury could be regulated under Section 402 either as a natural constituent of fish or as an unavoidable added contaminant.

The choice among these possibilities partly depends on whether mercury is properly considered "added" to fish. To FDA, it is indeed added, because its presence is the "result of environmental, industrial, or other contamination," and because FDA does not consider mercury to be an inherent constituent of fish. 12/ FDA's view that mercury is an added substance has been sanctioned by a federal court. 13/ More recently, however, another court has ruled that some mercury may not be properly considered added to fish, because some unknown portion of the mercury was not "artificially introduced or attributable to the acts or intervention of man." 14/ The definitional problem is not resolved in the Act itself, nor would it appear easy to determine the extent of contamination resulting from human action. The question now is on appeal.

Several federal agencies besides FDA are potentially involved in the control of mercury contamination occurring in waters. Under the Rivers and Harbors Act of 1899, the Army Corps of Engineers licenses the discharge of waste into navigable U.S. waters. 15/ The Federal Water Quality Control Act authorizes the Interior Department to take action against polluters whose discharges affect water quality. 16/ The Justice Department has initiated lawsuits against corporations allegedly responsible for mercury pollution. 17/ Another agency concerned with mercury pollution is the Environmental Protection Agency, which may establish tolerance levels for mercury pesticide residues. 18/ The Agriculture and Commerce Departments, as well as FDA, conduct voluntary inspection related to fish. 19/ Even the Office of Emergency Preparedness has been involved in sampling and analyzing mercury in water. 20/ Nevertheless, the powers of direct food safety regulation are concentrated in FDA, and any overlap in jurisdiction affects such areas as inspection and water standards rather than establishment of permissible mercury levels in edible fish.

Determination of Risks for Regulatory Purposes

Factors included in the risk determination are the concentration of methylmercury in fish, the minimum clinical effect level (MCEL) of methylmercury in human blood at which humans experience the adverse health effects, the daily intake level necessary to achieve the MCEL, a safety factor, and the reasonably highest level of fish consumption among U.S. populations. The recent court decision did not uphold the FDA's 0.5 ppm action level but rather favored a 1.0 ppm level based partly on the court's disagreement with FDA over the correct MCEL and the appropriate safety factor. 21/

Regulatory consideration of the risks of mercury may involve some factors that cannot be quantified. One such factor is the possibility that the level of methylmercury contamination of fish has remained relatively stable during millenia of human consumption, 22/ so that any risk is not necessarily a new or alarming phenomenon. Another factor is the lack of evidence of any large outbreaks of acute mercury poisoning in the United States, so that the experience in Japan and Iraq perhaps should not be given great weight in framing a regulatory approach to mercury in fish in this country. Neither, however, can the scale of the Japan or Iraq episode be ignored. Moreover, FDA has learned from the case of mercury that public concern sparked by new discoveries can provoke questions about why the agency had not acted earlier to reduce exposure to the possible risk. 23/

Setting Limits

The costs of a regulatory limit on the amount of mercury in fish fall most heavily on certain populations, just as mercury risks may affect some groups more strongly than others. Workers in the swordfish industry and their families possibly have the most to lose from regulations that set low permitted levels of contamination. Regional clustering of fishermen and industry suggests at least the possibility that food safety regulation can produce disproportionate effects among regions. Also affected are particular consumers. People who enjoy eating swordfish, for instance, could object to restrictions on swordfish availability that were designed to protect them from risks that they might knowingly wish to accept. Such consumers conceivably could complain that their chosen diet was being altered only because they are relatively few in number when compared to consumers of aflatoxin-contaminated corn or peanuts, for example.

The breadth of interests involved and the uncertainty over risks makes the setting of mercury limits far less than automatic. FDA has resorted to the interim device of an action level, rather than a formal tolerance partly for procedural reasons.* 24/ This course may be prudent, because the climate of opinion surrounding mercury regulation could change as a result of more scientific evidence or political and economic effects.

The mercury case also suggests the importance of coordination of FDA initiatives with efforts in the private sector. Following the emergence of concern in 1970, industry voluntarily withheld approximately four million pounds of fish from the market, and a recall of 832,000 pounds between December 1970 and May 1971 prevented FDA from having to seek a court-ordered seizure. 25/ In a rare exhortation to the public, FDA in 1971 also publicly advised against swordfish consumption. 26/ These actions had a severe impact on the swordfish industry. 27/ Thus, the mercury example indicates that effective food safety regulation involves more than a determination of when to ban or set limits.

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*The difference between action and tolerance levels is discussed more fully in Chapter 2, in the section on contaminants.

Issues

The widespread natural occurrence of mercury, the nutritional value and popularity of fish, and the wide range of mercury's industrial uses make control of methylmercury levels in foods a complex problem. Total elimination of methylmercury from the food supply would be desirable--given the fact that mercury itself affords no benefit in food and poses a threat to health. The likelihood of total elimination in the near future, however, is small because of the natural source of some contaminating mercury. Containment of its risks, therefore, involves several factors, including reduction of effluvial loss of mercury from industrial sites, careful monitoring of mercury levels in the general environment, and the establishment of appropriate standards for methylmercury content of various foods.

1. The mercury case illustrates a recurring problem in environmental regulation: a toxic material can enter the environment through different routes, each of which may be regulated by a different agency or not regulated at all. Although mercury in edible fish is regulated, appropriately enough, by FDA as a food

safety problem, that problem can be diminished through effective regulation of industrial waste, which requires the cooperation of different agencies. Mercury thus illustrates the need for continuing coordination among agencies that regulate environmental safety.

2. Other issues presented by the mercury illustration involve difficulties in determining the magnitude of risk for regulatory purposes. Methylmercury is highly toxic, as shown by the Japanese experience, but severity of risk may depend upon dose consumed.
3. Assessment of benefits, including industrial uses of mercury, the economic impact on the fishing industry, the desire of some consumers to eat fish, and the nutritional value of contaminated food, is difficult. The current statutory scheme does not explicitly provide for an assessment of benefits for added contaminants. FDA interprets the law as permitting a broad assessment of benefits including those of the contaminated food.
4. Both the assessment of risks and the assessment of benefits are complicated by patterns of distribution. Exposed fetuses and people who eat large quantities of contaminated fish are among the populations at highest risk. The fishing industry and people who live in areas where fishing is economically important have a particularly large interest in the benefits of the commodity. Tolerance or action levels effectively apply to all populations, but presumably should be based on some understanding of the effect of risks and benefits on special populations.

5. The mercury example raises the issue of whether a different standard of safety should be applied to a substance that has been contained in foods for a long time, than to a relatively new substance. People apparently have been eating mercury-contaminated fish for a very long time, believing it to be safe. A regulatory agency may be reluctant to impose its own judgment regarding the lack of safety in a way that would force a substantial change in long-standing dietary patterns. Yet an agency also cannot ignore new evidence of risks. The dilemma could be reduced if the statute were altered to permit a wider range of regulatory options, such as reliance on information dissemination. (In response to immediate concerns in 1971, FDA did warn against swordfish consumption; but warnings or other forms of information dissemination are not explicitly authorized by the statute,* and warnings alone might not suffice as a mechanism for regulating a food product in the long term).
6. The current statute also creates a problem of classification. Mercury in fish poses the same risks to human health regardless of the regulatory category it is placed in. But the applicable regulatory procedure and standard of safety depend on whether mercury is defined as an "added contaminant" or a "natural constituent." The present classification scheme may be implicitly based on the idea that the benefits of each category are qualitatively different from the benefits of other categories, so that the applicable regulatory standards and procedures are not related to magnitude of risk.

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*See Chapter 9.

7. Procedural complications in regulation also appear in the regulation of mercury in fish. FDA to date has chosen to limit the amount of the contaminant allowed in fish through action levels rather than formal tolerance levels. It is easier procedurally to establish an action level, but, as recently happened to FDA's mercury action level, a court can overturn an action level by substituting its judgment of the risks for the judgment of scientists whose assessments are used by FDA. Tolerance levels, in contrast, are set through cumbersome procedures* and must be sustained in court if they are supported by substantial evidence. Under current law, tolerance levels may not be set through notice-and-comment rulemaking, which allows for public participation yet does not involve cumbersome requirements.

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*See Appendix BB, pp. 32-34.

CASE ILLUSTRATION: NITRITES

Nitrite was selected as an example of an intentionally added substance for which there is no approved substitute and which may be carcinogenic either directly or by conversion to other substances (nitrosamines). Intentionally added nitrite may provide benefits by reducing the risk of botulism and by producing color and flavor. Nitrite also illustrates the regulatory problem presented when an increment of a potentially harmful substance is added to already existing sources, attributable both to the natural environment and human activity. The regulatory issues also are complicated by jurisdictional overlap between FDA and the U.S. Department of Agriculture.

Background

Nitrate salts such as saltpeter have been used in the curing and preservation of meat for centuries. After it was discovered in the 1890s that preservation of meat color was due to nitrite derived from nitrate, the direct addition of nitrite came into practice. Today, sodium nitrite is used in processed meat (particularly in pork), in processed fish and in poultry, as well as in some imported cheeses and pet foods. Nitrite is used in certain minor steps in processing other food products such as spray-drying of egg white, casein and soy protein isolates. Nitrite is also used in the home curing of meats.

Under experimental conditions, nitrite has been shown to have valuable properties in preserving meats as well as properties that retard the growth of the bacterium Clostridium botulinum. This bacterium produces the extremel potent toxin that causes botulism. These well established attributes of nitrite (whether added directly or derived through the addition of nitrate) have been reappraised in recent years as new scientific evidence concerning possible risks to human health from nitrites has accumulated.

Assessment of Risks

The amount of nitrite added to foods represents only a small fraction of the total daily exposure to nitrite of a normal adult on a regular diet. Nitrite is a natural constituent of human saliva; it is produced by the reduction of nitrate to nitrite by bacteria in the mouth. Bacteria also form nitrite from ammonia and other compounds naturally present in the human intestinal tract.

Dietary nitrate is absorbed and becomes the source of salivary nitrite. Nitrate in food may occur either as added nitrate salts or as natural food constituents. Some foods are naturally high in nitrate content: spinach, celery, lettuce, radishes, and beets can contain over 600 ppm nitrate-nitrogen. 1, 2/

In a recent report prepared by the Panel on Nitrates of the Environmental Studies Board of the National Academy of Sciences 3/ health effects of nitrate, nitrite, and nitroso-compounds are reviewed. Several estimates of sources of nitrite and nitrate for human beings have been reported. White 4/ has estimated that the average person in the U.S. ingests about 100 mg of nitrate and 11 mg of nitrite per day. Vegetables account for about 85 percent of ingested nitrate. For nitrite, saliva provides about 75 percent of the daily load, while cured meats provide about 21 percent. Tannenbaum *et al*. 5/ reported that the nitrite concentration in saliva of about 100 people was from 6 to 10 ppm. As a result of bacterial reduction of nitrate to nitrite, the nitrite concentration in saliva increases after a person consumes vegetables containing relatively high concentrations of nitrate. 6,7,8/

Tannenbaum 9/ estimates the total daily exposure of an average adult to nitrite is as follows:

Source	Nitrite Exposure mg/day (distribution)	Percent of Total
Food additive nitrite	3	3
Salivary nitrite	15 (10-20)	15
Intestinal nitrite	90 (65-100)	82

Based upon nitrate balance studies and the nitrite and nitrate analyses of fecal and ileostomy samples from a small number of subjects, Tannenbaum *et al*. 10/ estimated the intestinal formation of nitrite from ammonia and other organic nitrogen-containing compounds by bacteria to be 80 to 90 mg per day. The preliminary study indicated a considerable individual variability in urinary nitrate excretion and variability in the same individual from day to day on a protein-free diet. Tannenbaum hypothesizes most of the nitrite produced in the intestine would be absorbed into the blood and be oxidized to nitrate. The nitrate in blood is then excreted in the urine or secreted into the saliva where it may be reduced again to nitrite by bacteria. On the basis of Tannenbaum's calculations, the nitrite produced in the lower gastrointestinal tract is approximately 25 times that ingested as nitrite added to foods. The significance of the finding of nitrite formation in the intestine has yet to be fully evaluated, particularly in regard to its applicability to normal persons.

Health Risk from Nitrite*

While acute nitrate poisoning has not been reported in adults, infants may be subject to a serious condition known as methemoglobinemia if they ingest excessive amounts of nitrates. The gastric contents of infants under three months may have a pH above 4, a value that is higher than normal adults. The less acidic conditions may favor the presence of nitrate-reducing bacteria, which form nitrite, in the upper gastrointestinal tract. Nitrite is rapidly absorbed from the stomach into the blood, where it can oxidize the iron of red cell hemoglobin to methemoglobin, a derivative ineffective in oxygen transport. Episodes of methemoglobinemia in infants have generally been caused by high concentrations of nitrate in well water, rarely from nitrate-rich foods. 3/

Nitrite can also react with various nitrogen-containing compounds (secondary and tertiary amines, nitroso compounds, pesticides, ureas, carbamates and bisubstituted amides) in vitro and in vivo to form nitrosamines and nitrosamides, many of which have been shown to be carcinogens of high potency in experimental animals. In a recent review, Magee et al. 11/ list more than 100 nitrosamines of which more than 80 are carcinogenic in experimental animals. Nitrosamines are among the most versatile and potent known animal carciongens and as such are highly suspect as carcinogens in humans. 12/

The chemical reactions and conditions for nitrite reaction with amines to produce nitrosamines are well understood. For example, nitrosamine formation is favored by frying nitrite containing foods at high temperatures. Fried bacon is therefore more likely to contain nitrosamines than many other products. The kinetics and effects of many other agents that catalyze

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*See Chapter 5 for a general discussion on concepts for assessing risks.

(thiocyanate, bromide, chloride) and inhibit (ascorbic acid, gallic acid, tannic acid, glutathione, urea) nitrosamine formation have been extensively studied. 13/ The feeding of nitrite in combination with certain amines, amides, and ureas to rats or mice also produces malignant tumors. 14 a-m/ Inhibitors of nitrosamine formation (e.g., ascorbic acid) are of special interest, since their incorporation in the diet of experimental animals can effectively prevent cancer formation by nitrites in combination with any one of many amines. 13,15/ The demonstrated toxicity and carcinogenicity of nitrosamines in animals are a cause for concern in that ingested nitrite in humans may react with amines from the food, drugs, or from endogenous sources in the body to produce compounds of this type in vivo. There have been relatively few epidemiologic studies to date and none of these have clearly implicated nitrite or nitrosamines as the cause for esophageal or stomach cancer in humans. 3/

Recent studies by Newberne raise further question about the safety of ingested nitrite. In an analysis tangential to their primary experiment, Shank and Newberne 16/ observed that 27 percent of rats fed diets containing 1,000 ppm sodium nitrite developed tumors of the lymphoreticular system, compared with 6 percent of the control animals. However, because it was a tangential study, only a small number (96) of animals was tested. Using a much larger series, Newberne 17/ in unpublished data, recently reported the effects of feeding sodium nitrite to Sprague-Dawley rats in various diets and in the drinking water at various levels: 0, 250, 500, 1000, and 2000 ppm. In total, 48 of 573 (8.4%) of the untreated rats, and 172 of 1,380 (12.5%) of the nitrite-treated rats developed lesions diagnosed as lymphoreticular tumors. The differences are statistically significant,

$p < 0.01$. It was also observed that an "immunoblastic cell proliferation" of lymphoid tissues occurred in 40 additional rats of the control group, and in an additional 155 rats of the experimental groups. There was no clearly defined dose-response relationship in tumor responses to nitrite feeding. The investigator concluded that the nature of the observed tumor was different from that expected from nitrosamines, suggesting that nitrite had a direct carcinogenic effect of its own, not dependent on its conversion to nitrosamines. These unpublished data indicate only a marginal effect of nitrite on the lymphoreticular lesions, and their meaning is still unclear.

The significance of these findings in rats regarding human risk from ingested nitrite is uncertain at this time. One of the problems is the biological nature of observed lesions, because RNA viruses may cause lymphomas in rodents and some other mammals.* The presence of tumors of this type in appreciable numbers of control animals does not preclude that nitrite acts in some way to permit a higher expression of this lesion by decreasing natural defense mechanisms of the immune system.

At present, it is unclear from the evidence whether nitrite, at average consumption levels as a food additive, is a hazard to human health. Nitrite is a potential source of nitrosamines, that have demonstrated adverse biological effects when fed chronically to rats. These considerations are sufficient to assess the advisability of continuing the current levels of use of nitrite as an intentional additive if exposure from this source can be reduced or replaced by other acceptable agents.

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*If an infectious agent were implicated in the production of lymphomas, the statistical significance of the results might be altered. For example, the number of cages could become an important factor in the statistical analysis. However, it is very difficult to provide adequate controls for infectious processes of this kind. This problem is common to experiments of similar nature and design.

Assessment of Benefits*

There are at least three known benefits obtained from nitrite and nitrate in foods:

1) Nitrite inhibits or retards the germination and growth of Clostridium botulinum. This anaerobic bacterium can produce an extremely potent toxin responsible for botulism, a serious and often fatal disease in humans. The extent to which nitrite is needed as an anticlostridial agent in commercially processed foods is not yet fully known. However, there is no substance available that displays the antimicrobial effects of nitrite. Other possible approaches to controlling botulism (e.g., use of radiation, freezing, processing variations, or other preservatives) should be actively investigated.
2) Nitrite may provide a non-health benefit when used as an enhancer of color and flavor for processed and packaged meat and meat products. It is unknown how consumers would respond to such products lacking the familiar pink color and the characteristic flavor.
3) Nitrate is added to the environment as fertilizer. This use increases the amount of nitrate present in some water, and also increases the nitrate levels found in some vegetables. Additionally, vegetables, such as spinach and beets, which naturally contain high concentrations of nitrate, are widely consumed foods. Thus, these beneficial effects of nitrate-

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*See Chapter 6 for a general discussion on concepts for assessing benefits.

containing foods would need to be considered if an overall attempt to reduce human exposure to nitrate and nitrite were made.

Regulatory Considerations

Regulation of nitrite use in meat and poultry has been and remains complicated as a result of joint FDA-USDA jurisdiction, the different purposes of nitrite use, and the complex statutory classification scheme. Nitrite regulation may be at a crossroads, due to concern about evidence from the recent Newberne study on risks and about the confused regulatory situation.

The history of federal regulation of nitrite began in 1908, when USDA authorized its use in meat products in a regulation issued under the authority of the 1906 Meat Inspection Act. 18/ Historically, meat and poultry have been treated separately from other foods in legislation, and USDA now shares authority over meat and poultry safety with FDA. In the 1920s, USDA studied nitrite consumption because industry desired to use nitrites to color meat, because scientific investigations had revealed that nitrites could prevent botulism, and because safety concerns had emerged. USDA then authorized a maximum level of 200 ppm in meat and meat products, although higher levels in a few instances have been detected in analyses of meat samples. 19/ This level never has been changed formally, except for bacon. In bacon, USDA now permits 120 ppm of sodium nitrite. 20/ The limit in poultry is currently 200 ppm. (These limits are calculated as sodium nitrite; slightly higher levels would apply to potassium nitrite).

Classification

The regulatory status of nitrite in both meats and poultry is unclear. Because FDA and USDA apparently agree that use of nitrite in meat was sanctioned by USDA before the enactment in 1958 of the Food Additives Amendment, nitrites in meat have not been classified as a food additive under the Federal Food, Drug, and Cosmetic Act, and therefore have not been subject to the Amendment's safety provisions (including the Delaney Clause) affecting food additives. Neither has nitrite ever been regulated under the Act as a color additive; under the statutory definition, any non-agricultural, synthesized, or derived food substance that "is capable (alone or through reaction with other substances) of imparting color" to the food qualifies as a color additive. 21/ However, USDA has approved the use of nitrite in poultry to fix color. 22/ Nitrite for use as preservatives has not been explicitly recognized in regulations by either agency, nor has USDA issued labeling requirements mandated by the Wholesome Meat Act of 1967 for the use of artificial colors or chemical preservatives in meat. The purpose for which nitrite is used, such as coloring or preserving, is important for regulation because levels must be set with due regard for the amount of the substance needed to achieve the intended effect, and different levels might be needed to obtain different effects.

Both FDA and USDA take the position that nitrite use in bacon is prior sanctioned. Even if it is prior sanctioned, the level of permitted concentrations could be reduced through application of Section 402 of the Federal Food, Drug, and Cosmetic Act. 23/

Concerning nitrite in poultry, FDA and USDA have had different impressions in the past with regard to whether nitrite use had been prior sanctioned by USDA. USDA has concluded that nitrite use in poultry was not prior sanctioned. Given the different criteria applicable to some of the categories of food substance under the Act and the multiple uses of nitrite that cure, color, and preserve, options for regulation of nitrites in poultry are confusing and complex. Any decision on nitrite regulation presents difficulties in interpreting a complex Act for purposes of applying it to a particular substance with unclear benefits and risks.

Determination of Risk for Regulatory Purposes

The present Act would create difficulties in regulating nitrite even if the health effects were clearly known. But the case of nitrite involves various scientific factors that could bear on a determination of risks. For example, animal studies that have purported to demonstrate a risk of cancer have been conducted by only one laboratory, leaving replicability in question. Greater human exposure to nitrate in vegetables than to nitrite added to meat and poultry makes it difficult to delineate the risk of the added nitrite for regulatory purposes.

Finally, it has been suggested that discontinuation of the use of nitrite in meat and poultry may produce greater health risks--from botulism--than continued use. However, the magnitude of both sets of risks is extremely uncertain, because of the ambiguity in results of the animal tests, difficulties in applying animal test results to humans, the unknown extent of the botulism risk from meat and poultry in the absence of anticlostridial measures, and the potential feasibility of alternative anticlostridial measures such as freezing or the use of other chemicals which have diverse effects. Ascorbate, isoascorbate, and tertiary butylhydroquinone (TBHQ) have been found to block nitrosation, although their effects on botulism inhibition remain unclear.

Setting Limits

Solely for historic reasons, the prospect is raised that for regulatory purposes, the same level of nitrite could be considered safe in some meat but not in poultry. As a case illustration, nitrite presents the question of whether the statutory classification scheme sometimes operates to inhibit reasonable and acceptable regulatory decisions.

Attempts by USDA and FDA to regulate nitrite in meat raise some very difficult statutory and practical problems. For example, if the regulatory objective is to ban carcinogens, does this objective require the banning of substances that may not be inherently carcinogenic but are converted into carcinogens in cooking or digestion? Another question is whether FDA currently has authority to set action levels for nitrite, or to phase out its use.

Issues

1. In the case of potentially hazardous substances that are both naturally occurring and deliberately added to foods, total body burden of the substances needs to be considered before tolerance levels and other regulatory measures are applied. It is important also to assess the incremental risk attributable to the added substance.
2. Because the body burden comes from several sources through different routes, meaningful regulation must take into account the aggregate

health effects. Therefore, regulation of these compounds should be coordinated. Currently, regulation may be fragmented as a result of intricacies of the statutory classification system. Effective regulation also requires close cooperation between agencies with authority to regulate these substances.

The law creates some technical legal distinctions among substances based on the intended uses. For example, a substance used both as a food additive and a color additive must be approved separately for each use. Therefore, the question arises as to how to regulate nitrites, which have multiple uses.

3. An important consideration in the source of nitrite is food processing. Certain food processing techniques, such as the spray-drying of egg whites, casein, and soy protein isolates, yield products containing up to 50 ppm nitrite. 24/ If lower limits were set on the amounts of nitrite permitted in such products, time, expense, and new processing technology would be required.
4. Interpretation of test data poses a sensitive problem in nitrite regulation. Recent evidence of the carcinogenicity of nitrite was obtained in two investigations, but both were conducted by the same investigator and have not been confirmed independently.
5. An example of a special population at potentially higher risk is neonates who can develop methemoglobinemia from nitrite ingestion. The relevant scientific issue concerns the source of the nitrite. The regulatory problem extends to deciding how much weight should be accorded to a risk that may affect only one discrete population.

6. From a regulatory viewpoint, the consideration of benefits presents a multifaceted challenge in the case of nitrite. Apparent health benefits result from the role of nitrite in inhibiting C. botulinum. The value of these benefits involves the question of whether there are other ways of preventing botulism. Health benefits and the availability of substitutes are not regulatory criteria explicitly authorized by the statute, and their consideration in evaluating food additives may in fact be illegal under the statute.

   The economic and other non-health benefits (such as gustatory pleasure) of substances with a long history of use are recognized implicitly in the law by the exemption of prior sanctioned substances from the safety requirements applied to food additives. There may be costs to the meat and poultry industries that could result from withdrawal of nitrite. Thus, a consistent regulatory policy must include whether, and how, to consider these benefits. Currently, the complex statutory classification scheme and the differing provisions governing the benefits of food substances make it virtually impossible to predict which benefits will be considered, and to what extent, in devising future nitrite regulations.

CASE ILLUSTRATION: AFLATOXIN

Aflatoxin was selected as an illustration of a known carcinogen that enters food as a consequence of the manner in which foods are grown, handled, or stored. Aflatoxin is not a deliberate food additive, but occurs as a natural contaminant in such common foods as peanuts and corn.

Background

Aflatoxin is a generic term referring to a group of highly toxic compounds produced by the fungus, Aspergillus flavus/parasiticus. 1/ In addition to the original recognition of aflatoxins B_1 (AFB_1), B_2 (AFB_2), G_1 (AFG_1), and G_2 (AFG_2), there also have been a large number of metabolites whose structures have been elucidated. 2/ These are mostly produced in mammalian tissue upon ingestion by the mammal of the parent compound AFB_1, although some may also be produced by the fungus or by chemical treatment of AFB_1. Of the four original aflatoxins, AFB_1* is the most common, usually comprising about 90 percent of the aflatoxin residues observed on contaminated foodstuffs; it is also the most toxic. Thus, most of the experimental work has been undertaken with this compound. This is an acceptable approach not only because of AFB_1's predominance, but also because its biological activity is qualitatively similar to the remaining aflatoxins. The rest of this discussion will therefore focus on AFB_1, with an understanding that a small additional contribution of toxicity may be provided by the other aflatoxins.

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*Aflatoxins are derivatives of difurano-coumarin cyclic compounds and contain five fused ring systems. 3/

Although *A. flavus* and *A. parasiticus* are clearly related morphologically and taxonomically, most of the literature refers to *A. flavus*. 4/ This organism is found worldwide in climates ranging from the temperate to the tropical. It is generally considered to be soil-borne, although edible foods grown above and below the soil surface may harbor its growth. The conditions that favor growth include moisture and warm temperature, thus suggesting a more proliferative growth in tropical areas. However, the mold may also grow in drier climates because of the presence of moisture that may be retained in improperly dried individual seeds and fruits.

Peanuts were the first food product to have been found to be contaminated. 3/ In recent years, corn has also been discovered to be an important source of aflatoxin. 5/ In addition, other foods including pistachio nuts, cottonseed, copra, and yams have been implicated. A large variety of foodstuffs have been analyzed and those identified above are the major ones that showed significant residues.

Levels of contamination may range from the lowest detectable level (less than 0.1 ppb) to several thousand ppb in certain peanut and corn samples. 5/ The distribution of aflatoxin within a lot of a particular commodity may be extremely varied and may present difficult sampling problems for the analyst. Oftentimes, 90-99 percent of the individual nuts or kernels may be free of aflatoxin while 1 percent or less may contain as much as a million ppb. 6/ If these highly contaminated kernels are ground or processed with the clean kernels, a high average of aflatoxin may result; thus it becomes important for the analyst to find these few contaminated kernels. The wide variance in contamination among kernels is no doubt caused by occasional kernels becoming more susceptible to fungal invasion because of insect or mechanical damage.

Many people have assumed that aflatoxin has always been a contaminant of these foods. However, not all subscribe to this view. The recent introduction of certain mechanical harvesting machinery and newer varieties of plants with an altered resistance to the mold or its predisposing vectors may have played a role in increasing the level of contamination. Some limited research efforts have been directed towards the development of crop varieties that would possess higher resistance to the A. flavus organism. 7, 8/

Much research has been concerned with the removal or destruction of aflatoxin in food commodities. 9/ In general, the best control is prevention through proper harvesting and processing procedures, although variable quantities of aflatoxin may, under certain conditions, occur in the field prior to harvest. 5/ For example, electronic sorting of individual peanut kernels rejects highly contaminated kernels because of fluorescence associated with contamination. Control of imported commodities through inspection and chemical analyses has been another useful method to insure low levels in marketable products. Several procedures using chemical solvents to extract or otherwise degrade the aflatoxin residue have been developed and tested. Whereas these may be useful for animal feed products, they have not been generally accepted as methods for producing a safe, nutritionally unaltered product for human use. The extraction of oil from the food commodity also extracts the aflatoxin, but marketable cooking oils produced from corn and peanuts do not contain aflatoxin residues because most oils are alkali-refined which effectively destroys the compound. Heat used in the cooking process may destroy, under certain conditions, some of the aflatoxin, but it cannot be relied upon for routine use either commercially or in the home.

A relatively recent concern has been the presence of aflatoxin residues found in products from animals fed feedstuffs containing aflatoxin. 10/ Milk that may contain AFM_1 is of concern because the product is consumed by children. However, the levels of aflatoxin in animal products are usually much lower than those associated with plant food commodities; and the known aflatoxin metabolites in milk and meat products are less toxic than the parent compound. 2/

Biological Effects

Animal Studies - Nearly all of the literature on the biochemical parameters associated with aflatoxin toxicity has been derived from laboratory and domestic animal studies. 11/ The manifestations of this toxicity may result either from a large dose consumed over a short period of time or smaller doses consumed over a longer period. The large dose consumed over a short period elicits an acute toxic response (aflatoxicosis) usually characterized by bile duct proliferation and periportal fibrosis of the liver, gastrointestinal hemmorrhage, and death. The quantity required to elicit this reponse varies widely between species and depends on the dosage route; it is usually measured as the milligrams required to be lethal for 50 percent of the test population (LD_{50}). The LD_{50} range is approximately 0.3 - 18 mg/kg of body weight and designates this compound as extremely toxic. It is important to note that this type of toxicity is not usually observed under practical conditions and is almost always associated with animal feeding.

The far more significant toxicity caused by AFB_1 is the hepatocellular carcinoma (liver cancer) observed in almost all of the laboratory animal species that have been tested. 1/ The test quantities are usually measured as parts per billion (ppb) in the diet, which represent exceedingly small amounts. Laboratory experiments have shown that the AFB_1 required to cause tumor induction in a significant number of animals ranges from somewhat less than 1.0 ppb for the rainbow trout to levels in excess of 2,000 ppb for the mouse and non-human primates, a several thousand-fold difference. AFB_1 is the most potent carcinogen known in laboratory animals, as demonstrated experimentally. It may be of significance to note that some species of non-human primates appear to be relatively resistant. However, because of the long life span of primates (e.g., about 15 years for the rhesus monkey) the available studies may not have been long enough to detect development of tumors and thus may have precluded an effective analysis of the relative carcinogenicity for this group of mammals.

Human Studies - Documented cases of human aflatoxicosis (acute toxicity) are relatively rare. 12, 13/ Of those cases for which there was reasonably good documentation, children appeared to be more susceptible —a characteristic common to the young of any species. These data were obtained from India and Africa where accidental ingestion of aflatoxin contaminated foodstuffs occurred. Death occurred in some cases and was usually associated with liver involvement; a form of hepatitis was observed in one group of 100 children and adults (ages 5-30), who died over a several week period following consumption of an estimated 2-6 mg of aflatoxin per day. A general survey of these several reports would suggest that levels of aflatoxin of about 0.1 - 0.6 mg/kg body weight consumed for several days or more is capable of causing an acute toxic response culminating in death in humans.

In addition to these reports, there have been a number of suggestions and some experimental evidence with non-human primates that Reye's syndrome* might be an expression of acute aflatoxicosis; 14/ this has not been confirmed, however.

Rigorous proof that AFB_1 is a human carcinogen is not available. However, several epidemiologic studies suggest that aflatoxin may be a potent human carcinogen when potency is measured in terms of the quantity of chemical required to elicit the toxic response. The evidence comes from Asian and African population studies. 15/ This evidence is derived primarily from the correlation between the level of aflatoxin ingestion nanograms per kilogram body weight per day (ng/kg/day) and the incidence of primary liver cancer in four geographical areas (Kenya, Swaziland, Thailand, and Mozambique). Males showed a higher incidence of liver cancer than females; this finding is consistent with the higher susceptibility observed in male laboratory animals. However, similar studies in the U.S. have not demonstrated such an association between aflatoxin consumption and primary liver cancer. This lack of an association may be due to the extensive migratory pattern of people that confounds the data on past dietary practices and because of the much lower incidence of primary liver cancer in this country. A major weakness in comparing the African/Asian liver cancer incidence with the U.S. incidence is the likelihood that other factors—genetic, dietary and environmental—may predispose to liver cancer in Africa and Asia, and are quite different from such factors in the U.S. The African and Asian epidemiologic studies show that liver cancer incidence is substantially higher in the more tropical countries than the temperate countries. Presumably, in the temperate countries, control of harvesting and processing procedures are most rigorous and conditions for mold growth are less favorable. A conflicting interpretation of human epidemiologic studies in Africa, and possibly Asia, is that the incidence of primary liver cancer may be related not only to aflatoxin ingestion but also to infection with hepatitis B virus. This makes uncertain the relative importance of aflatoxin and hepatitis B virus in the genesis of liver cancer in humans and remains to be clarified. An additional confounding factor for the U.S. population is that most liver cancers are associated with cirrhosis of the liver. In turn, cirrhosis of the liver in the U.S. is associated with high alcohol consumption. Thus, it is not clear how much weight to give to aflatoxin itself as a cause of primary liver cancer in this country.

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*Children with Reye's syndrome usually have acute damage to liver and brain. In most instances a cause has not been identified.

In Vitro Studies - There have been a number of in vitro studies of AFB_1. 2/ These have been undertaken to evaluate fundamental biochemical mechanisms, mutagenicity, and characteristics of its metabolism by the "drug metabolizing enzyme system". The biochemical mechanism studies have demonstrated that AFB_1 possesses activity for a wide variety of systems; most notably, it alkylates DNA and alters various properties of the genome; this is consistent with AFB_1 carcinogenic activity. Moreover, AFB_1 has been demonstrated to be an extremely potent mutagen. 16/ The potent activity of AFB_1, both in vivo and in vitro, depends on its being metabolized by the drug metabolizing enzyme system.* This enzymatic reaction may either produce less toxic, more readily excreted metabolites, or a more toxic product generally referred to as the ultimate carcinogen and thought to be the 2, 3-epoxide. This latter reaction represents an activation and depends on the activity of the enzyme system. Of particular interest is the observation that this enzyme activity can be readily altered by various external "environmental" factors such as dietary nutrient intake. Thus, the intake of dietary protein, for example, significantly modifies enzyme activation and thereby may alter tumorigenicity for this compound. 17/

Assessment of Risks**

Assessment of risk associated with aflatoxin ingestion, as with any toxic chemical, relies on the estimations of human toxicity and the amount of material consumed. Aflatoxin ingestion in fact may be one factor influencing the frequency of primary liver cancer in the U.S. However, other factors in the etiology of liver cancer such as hepatitis B virus and alcohol consumption may confound any reasonable estimate of risk for primary liver cancer in the U.S. due to aflatoxin ingestion. 13/ Because of the contradictory nature of a number of recent risk assessments regarding aflatoxin and liver cancer in the U.S., detailed discussion of such assessments is not undertaken in this report. In spite of these analytical difficulties, prudence would nevertheless demand that aflatoxin intake be minimized—primarily on the strength of the linear relationship between level of aflatoxin intake and liver cancer incidence in the epidemiologic studies.

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*Also called the aryl-hydrocarbon hydroxylase (AHH) or mixed function oxidase (MFO).

**See Chapter 5 for a general discussion on concepts for assessing risks.

An overview of the estimation of risk for aflatoxin illustrates certain conclusions. First, the epidemiologic data, in terms of the impressive relationship between aflatoxin intake and liver cancer incidence, suggest aflatoxin as an etiologic agent but does not permit an accurate estimate of aflatoxin-associated cases of liver cancer in the U.S. without making major, and perhaps, unwarranted assumptions. More research on dietary and environmental factors that predispose to aflatoxin-caused liver cancer is obviously needed. Therefore, epidemiologic data, when available and interpretable despite confounding variables, would be the most appropriate predictor of human response.

Second, although aflatoxin is a potent carcinogen in rats, the data are difficult to extrapolate to human beings. For example, another experimental rodent species, the mouse, requires a thousand-fold greater level of exposure than the rat, and thus without a priori knowledge on the most appropriate animal model, extrapolation to human beings is not quantitatively possible, especially when these are the only data available.

Third, in spite of the potentially greater value of epidemiologic data, considerable caution must nevertheless be exercised when applying such data to estimate the health risk to an individual or to another population. Correlational studies, based on different populations, do not quantitatively describe risk for an individual due to the modification of the degree of risk from other external factors. Therefore, a body of knowledge, including data on animals, in vitro tests, and human epidemiologic studies are more valuable collectively than is any one group of data.

Assessment of Benefits*

The important principal food commodities vulnerable to aflatoxin contamination are corn and peanuts. The health benefits of these foods are very difficult to estimate. Perhaps the most significant contribution of these foods is that they are a source of calories and protein in the average U.S. diet. 18/ The protein content of peanut products offers an even greater potential benefit than is generally-recognized. On a weight basis, peanuts and peanut butter contain 4 to 7 times more protein than common snack items and 30 percent more protein than hamburger patties. Moreover, corn provides an additional source of fiber. Milk and dairy products provide highly significant quantities of energy (11.4 percent of total per capita intake), protein (22 percent), and calcium (74.5 percent). Meats provide large amounts of calories (19.9 percent), protein (41.6 percent) and vitamin B_{12} (70 percent).

The relatively low cost of protein in peanut butter (16¢/20 gm), hamburger (21¢/20 gm), and milk (24¢/20 gm) broadens availability of protein to a wider range of income groups.

However, quantification of these benefits is open to debate. Substitution of other foods would be costly but certainly not impossible. Yet clearly the risk would have to be very high to convince consumers to make a major change in their diet, given the widespread use of , and preference for the products involved. No simple regulatory rule can be applied to the problem of human aflatoxin exposure.

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*See Chapter 6 for a general discussion on concepts for assessing benefits.

Regulatory Considerations

In 1965, as a result of increasing concern about the relationship of liver cancer to consumption of peanuts and other aflatoxin-contaminated foods, FDA established a temporary limit, called an "action level", of 30 ppb of total aflatoxins in corn, peanuts, and other foods for human consumption. The agency reduced this permitted level to 20 ppb in 1969. 19/ In 1974, FDA proposed a formal tolerance level of 15 ppb. 20/ To arrive at these levels, FDA balanced the economic and practical feasibility of reductions in contamination against anticipated reductions in health risks. The proposed tolerance level of 15 ppb currently is pending, while the 20 ppb action level remains in effect.

Classification

One of the categories of food substances for purposes of regulation, according to the classification scheme suggested in Chapter 2, consists of unavoidable added contaminants. FDA regards aflatoxin as an unavoidable added contaminant of corn, peanuts, and other food. Section 406 of the Federal Food, Drug, and Cosmetic Act gives FDA specific authority to establish tolerance levels limiting the amount of such contaminants in food to the extent necessary for the protection of public health.

Contaminants can be considered unavoidable, under Section 406, if they "cannot be avoided by good manufacturing practice." Conceivably, aflatoxins could be considered avoidable in the sense that alternative foods exist to render consumption of aflatoxin-contaminated foods unnecessary. FDA interprets the law as authorizing the agency to determine only whether the contaminants are unavoidable in the food, not whether the food itself is thought to be a desirable component in people's diets. So aflatoxins are deemed unavoidable in certain foods because they cannot be eliminated through known feasible methods.

A more difficult question is whether aflatoxins are properly considered "added" to such foods as corn and peanuts for purposes of the statute. There is no statutory definition and no universally accepted test for determining whether a substance is "added" to a food for purposes of the Act. As was noted in Chapter 2, FDA maintains that a substance may be considered to have been "added" through the environment if it is not inherent in the food, whether or not human actions played a part. Some courts, in reviewing FDA actions, have suggested that only human intervention can cause a substance to be "added" in terms of the statute, while other courts have agreed with FDA. 21/ Unless and until courts instruct FDA differently, the agency can be expected to continue to regulate aflatoxins as an unavoidable added contaminant under Section 406.

Determination of Risks for Regulatory Purposes

Extrapolation from combined animal studies has led FDA scientists to the recent conclusion that in the Southeastern states, where consumption of aflatoxins is presumably greatest primarily because of the extent of contamination of corn, the annual incidence of liver cancer attributable to aflatoxins present in foods at the currently permitted level of 20 ppb is between 0.24 and 1.8 per 100,000 population. FDA considers this range to be generally consistent with valid results of epidemiologic studies of Swazi and Thai populations and with data from limited *in vitro* tests. 22/

The agency also attempted a Mantel-Bryan mathematical extrapolation* of the combined results of five rat studies, but this extrapolation produced results that indicated that the human beings is somewhat more resistant than the rat. The agency thus concluded that, insofar as liver cancer caused by aflatoxin consumption is concerned, "...humans are closer to relatively resistant species such as mice and monkeys than they are to the highly susceptible rat strains," such as male rats of the Fisher strain. 23/

Setting Limits

FDA has considered various factors, in addition to overall health risks and degree of unavoidability under current or feasible industry practices, in setting permissible levels for aflatoxins. Aside from assessment of estimated risk, another factor is the technology of analytic detection. Because FDA has found that currently feasible assay programs do not allow detection of fewer than 5 ppb aflatoxins in peanuts, the agency realistically cannot consider any lower level to be enforceable. A lower than 5 ppb level may be effectively unattainable because of the considerable variability of aflatoxin levels within and among peanut lots. An additional factor is that FDA believes that aflatoxins legal limits are much higher than, but proportional to, the average aflatoxin levels actually present in foods; at a 20 ppb legal limit, the actual level in peanuts is estimated at 2.0 ppb, while at a hypothetical 15 ppb legal limit the actual average level is predicted to be 1.5 ppb. 24/

Issues

1. Estimation of human risk from animal studies is relatively unreliable because of variations in the sensitivity of animal species

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*Appendix F describes this extrapolation technique.

that may differ by several orders of magnitude. Epidemiologic data, when available and interpretable, are theoretically the more reliable for estimating human risk. However, in the face of many confounding variables, it is difficult to interpret the available epidemiologic data with regard to aflatoxin ingestion and primary liver cancer in the U.S. population.

2. If the maximum amount of aflatoxin allowed in the diet is assumed to be 0.1 ppb, two questions follow. First, what level may be permitted in peanuts, corn and milk before the 0.1 ppb level in the total diet is exceeded? Second, how much lower can existing allowable levels of aflatoxin be reduced before the processing costs become prohibitive for widespread, low-cost use? Increased costs will, of course, have different consequences in different segments of the population, thus raising questions of social equity.
3. Different permitted levels of aflatoxin may be appropriate for different foods if human exposure levels could be documented.
4. In addition, though regulatory guidelines may be derived in a seemingly straightforward manner, there may also be unanticipated secondary effects. For example, when a regulatory guideline was set for aflatoxin contaminated cottonseed destined for human consumption, some of the contaminated material was diverted to animal feed which subsequently gave rise to AFM_1 contamination of milk. Thus, a primary regulation may generate an unanticipated second order effect. This emphasizes the importance of a comprehensive assessment of foreseeable regulatory outcomes.

5. In setting tolerance levels, consideration should be given to the diminishing returns in health benefits as a lower level of contamination is sought. For example, greater absolute health gains might result from a reduction from 20 ppb to 15 ppb than from 15 ppb to 10 ppb. The limited technologic capability to reduce contamination and the cost of such reduction also could make lower legal limits unwise.
6. The uncertainty over the health risks of aflatoxin consumption makes regulation difficult. Tolerance levels cannot now be established on the basis of scientifically certain information about the risk of liver cancer at different levels of contamination of corn or peanuts. This issue is especially troubling in the case of aflatoxin because aflatoxin has been extensively studied in epidemiologic, animal, and *in vitro* tests.
7. Section 406 of the statute requires consideration of the unavoidability of aflatoxin in corn, peanuts, or other foods. The law does not require consideration of the nutritional, economic, or other benefits of the food itself, although FDA has considered these benefits in the case of aflatoxin.
8. The case of aflatoxin presents the issue of so-called "technology-forcing" tolerance levels. One regulatory approach is to try to cause improvements in technology that affect safety by requiring a reduction that seems beyond industry's current capability. This technique is an option in many areas of environmental regulation, including not only food safety but also the fuel efficiency of automobiles and the level of exposure to hazardous substances in

the workplace. 25/ Modern technology-forcing regulation may be too new to allow regulators to predict with confidence whether it constitutes an appropriate approach in a particular circumstance, but in general it offers the possibility of using regulation to reduce risks without substantially reducing the benefits of a particular food.

9. Existing procedural requirements make regulation complicated and time-consuming. Efforts to give industry and other sectors of the public an ample opportunity to participate in different stages of the regulatory process has helped prolong a final decision on the 15 ppb tolerance level proposed by FDA in 1974. Due to procedural complexity and the need to justify a tolerance level with substantial evidence in order to survive judicial review, FDA so far has set action levels instead of tolerance levels on aflatoxin. Action levels can be established more expeditiously than tolerance levels, but are more vulnerable to being overturned in court. 26/ Also, action levels are set without substantial public input, so that their advantages in time and convenience are off-set by disadvantages of the lack of public participation and procedural safeguards.

FURTHER ISSUES RAISED BY THE FOUR CASE ILLUSTRATIONS

1. When acute toxic effects have been demonstrated for a food or food constituent, what steps are necessary to monitor possible chronic effects of sub-acute exposures? The problem is emphasized by mercury, aflatoxin and nitrite. It clearly relates both to carcinogens and other toxins and requires consideration particularly of neurologic and behavioral effects.
2. How should data from toxicologic studies on animals be extrapolated quantitatively to human beings? The problem is highlighted by saccharin and aflatoxin. Given clearly demonstrated differences in reactions of different species to particular toxins, how reliable an indicator are animal data in quantitatively forecasting human effects?
3. What role in determining regulatory policy should be assigned to epidemiologic and short-term or in vitro toxicologic tests? The problem of interpreting epidemiologic data is particularly striking in the case of aflatoxin and saccharin and of short-term tests in the case of saccharin. Can any single testing mode be reliably used for forecasting food hazards, or is a combination of different modes required? Should certain tests be used as screening devices to detect the need for more extensive testing?
4. How can exposure patterns be better estimated for regulatory purposes? The problem is clearly defined by the mercury and saccharin cases. How can consumption in the general population, or in subpopulations, be effectively measured? What is the range of consumption variation? What are the dietary combinations that may give

rise to high aggregate exposures? Are effects induced only at peak levels or are they cumulative at lower exposure levels?

5. Should levels of acceptable risk, rather than zero risk, be established as targets for food safety regulation? The problem is clearly brought out by aflatoxin and mercury where "natural" sources contribute importantly to reported effects. In determining acceptable risk, is the level of anticipated benefit a factor to be taken into account.
6. What form of assessment should health and non-health benefits receive in regulatory decisions? The efficacy of food ingredients need not be subjective. For example, direct additives such as some vitamins and minerals, have measurable beneficial effects. Moreover, efficacy can appear in anticipated and unanticipated ways, and methods to detect such effects need to be actively developed. Yet benefits in part are often a matter of individual preference. Therefore, when should benefits be subject to government decision? Where benefits can be assessed objectively, can they be quantified in commensurable terms with risks? Where and how should risk and benefit assessments be made and what part should they play in regulatory decisions? This critical set of questions arises in each of the four cases.
7. Food additives (such as saccharin) are similar to contaminants (such as mercury or aflatoxin) in that banning the substance would totally remove a food item desired by particular subpopulations. How should regulatory agencies deal with special subpopulations who may be differentially affected by regulatory action? How far

should equity considerations be taken into account? How should costs to protect high-sensitivity or high-impact subpopulations be allocated? These problems are illustrated by the mercury, aflatoxin and saccharin cases.

8. Should considerations other than health risks and benefits be included in regulatory decisions regarding food safety? Are economic factors such as employment and industrial profit appropriately introduced into decisions? These questions are clearly pertinent in all four cases which involve major components of the food supply.

These are examples of food policy issues drawn from the four cases. They are not exhaustive but they will be prominent in succeeding chapters. They will be addressed in the concluding chapter that summarizes the issues and committee recommendations.

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17. See U.S. Congress, Senate, Committee on Commerce, supra note 8, testimony of Albert Fritsch, p. 117.

18. See 40 C.F.R. 180.

19. Approximately 30 percent of all processed fish in the United States is inspected by the Seafood Quality and Inspection Division of the National Marine Fishery Service.

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25. Harvard Law Review, supra note 7, which advocates labeling rather than banning mercury-laden fish.*

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*See Chapter 7 for further discussion on labeling.

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20. 39 Fed. Reg. 42748 (December 6, 1974).

21. See Chapter 2, note 19 and accompanying text. The court in United States v. Boston Farm Center, Inc., Civil Action No. 77-43-THOM (M.D. Ga., December 7, 1977), held that aflatoxin was added to corn for purposes of the statute.

22. U. S., Food and Drug Administration, Bureau of Foods. Assessment of Estimated Risk Resulting from Aflatoxins in Consumer Peanut Products and Other Food Commodities. Washington, D.C.: Food and Drug Administration, mimeographed, January 19, 1978. Available for public examination, 43 Fed. Reg. 8808 (March 3, 1978).

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24. Ibid., pp. 18-19.

25. For example, in reviewing an occupational health regulation for vinyl chloride exposure, a court stated:

> In the area of safety, we wish to emphasize the Secretary is not restricted by the status quo. He may raise standards which require improvements in existing technologies or which require the development of new technology, and he is not limited to issuing standards based solely on technology already fully developed.

Society for Plastics Industry, Inc., v. Occupational Safety and Health Administration, 509 F2d 1301, 1308-1309, (2d Cir., 1975), cert. den. sub nom. Firestone Plastics Corp. v. Department of Labor, 421 U.S. 922 (1975).

26. In United States v. Boston Farm Center, Inc., supra note 21, the court did not apply the 20 ppb action level to corn, but instead enjoined the defendant only from dealing in corn that contained more than 100 ppb of aflatoxins. This decision, like other court rulings on substantive issues concerning action levels, is not controlling precedent.

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Chapter 4

CONCEPTUAL TOOLS FOR ASSESSING FOOD SAFETY POLICIES

The development of useful and consistent food safety policies requires systematic consideration of risks and benefits within a broad framework. This chapter begins by defining risks, benefits, and the concept of acceptable risk. It then distinguishes between risks to individual persons and risks to the public at large.

The remainder of the chapter describes a framework for the formulation of food safety policies in a broader context than is possible under existing laws and regulations. The framework entails consideration of the availability of substitutes in arriving at decisions about food additives.* It also allows for the development of discriminating policies based on the evaluation of an additive's risks and benefits in different uses and by different user groups and includes consideration of health and nonhealth benefits.

Definition of Risks and Benefits

The idea of "risk" is used frequently in everyday language--a risky investment, risky policy, risky voyage, etc. In both everyday usage and in technical discussion, "risk" is variously used to mean the severity of a potential misfortune, the probability of its occurrence, or to the notion that uncertainty is involved. In this chapter, the term "risk" refers to the probability of occurrence of an adverse effect of some specified nature and magnitude.

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*For simplicity this chapter discusses food additives. However, the concepts are applicable to other food substances, such as naturally-occurring toxic substances or contaminants.

The first step toward an appropriate policy for reducing a health risk is to determine, as objectively as possible, the nature and magnitude of the risk. To assess risk requires information that can be used to:

- define the conditions of exposure, including the amount of substance, duration of exposure, and the specific populations exposed;
- identify the adverse effects such as carcinogenesis, mutagenesis, teratogenesis or behavioral impairment;
- relate exposure to effect, such as by identifying dose-response functions; and
- estimate overall risks to individuals and to society as a whole by analysis of the foregoing points.

A method of categorizing risks could be helpful in developing and implementing a food safety policy. The number of categories should be large enough to be useful for policy purposes and small enough to be understandable to the general public. For example, high, moderate, and low categories could signify different levels of risk, taking into account the various factors described above. If the categories are broad and general, difficulties with borderline cases could be minimized, but some problems will remain with any categorization system.

The assessment of benefits, which are realized positive effects, of food substances is not as well developed as the assessment of risk, because benefits seldom take the form of countable episodes analogous to cases of disease or deaths. Ambiguous measurement notwithstanding, benefits are real, and may be physiological, psychological, or economic.

A food additive's health benefits may be direct or indirect. Direct physiological or nutritional benefits are the enhanced quality and safety of the food supply, such as would be caused by adding nutrients or extending shelf life. An indirect health benefit would be a reduction in some type of risk. For example, saccharin may reduce the risk to diabetics of excess sugar consumption. Risk reductions of this type are often difficult to measure precisely (see Chapters 5 and 6).

Psychological benefits are those perceived by consumers. Additives that improve taste, texture, appearance and odor of food can confer such benefits. The pervasive demand for sweeteners, including noncaloric ones, illustrates this point.

Economic benefits can result from additives that increase efficiency of food production, enhance preservation, or substitute for more expensive ingredients.

Acceptability of Risks and Benefits*

Subjective judgment is an inherent feature of decisions concerning acceptability of risks and benefits. 1,2/ A risk may be judged acceptable as a result of a conscious decision, based on a balancing of expected benefits and probable harm. Or a risk may be deemed acceptable because it seems less serious than other risks we accept. Various criteria may guide policymakers in judging acceptability, but the criteria themselves often are subjective. They include:

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*For a discussion of this concept see References 1,2,3,4/.

- Reasonableness. The concept of reasonable reduction of risk or "rule of reason" is pervasive in arguments on safety. The aim of safety judgments is to decide what is reasonable.
- Custom of usage. This is exemplified by the list of food ingredients "generally recognized as safe" (GRAS).
- Prevailing professional practice. This can develop from historical precedents.
- The presence of benefits. The 1969 White House Conference on Food, Nutrition and Health recommended that:

> No additional chemicals should be permitted in or on foods unless they have been shown with reasonable certainty to be safe on the basis of the best scientific procedures available for the evaluation of safety and meet one or more of the following criteria:
>
> 1. They have been shown by appropriate tests to be significantly less toxic than food additives currently employed for the same purpose.
> 2. They significantly improve the quality or acceptability of the food.
> 3. Their use results in a significant increase in the food supply.
> 4. They improve the nutritive value of food.
> 5. Their use results in a decrease in the cost of food to the consumer. 5/

Individuals, society, and governmental agencies often differ about benefits justifying the risks in any particular instance. Previously agreed upon decision rules such as the Delaney clause illustrate such differences (see Chapter 2). Some believe that the clause has been an effective deterrent to a serious identifiable risk, and advocate its extention to mutagens and teratogens as well. Others criticize it for precluding any consideration of benefits and for possibly diverting attention from other, more serious risks.

Acceptable Risk and the Role of Government

Most persons make risk judgments because almost all aspects of daily living entail some risks. 6/ Usually, there is a presumption that individuals can decide which risks they find acceptable. In some instances, however, a governmental role may be appropriate even though it pre-empts individual judgment. The nature of the risk, in part, determines whether individuals may make their own assessments of its acceptability, or whether a societal (governmental) decision should be made to limit the individual's exposure to risk. A list of some of these risk characteristics 1/ is in Table 4-1. In general, risks characterized by the descriptions on the left side of the table are deemed appropriate for individual assessment. The case for government intervention is stronger for risks that are described more accurately by the right side of the table.

One case for government intervention may be made when individual decisions affect the safety of others. 7/ In dealing with contagious diseases, for example, an individual may be willing to accept the risk of disease but the government may insist on vaccination to protect the collective welfare. 8/

Table 4-1. An Array of Factors that Influence Risk Judgments.*

Risk assumed voluntarily	Risk borne involuntarily
Effect immediate	Effect delayed
No alternatives available	Many alternatives available
Extent of risk known with certainty	Extent of risk not known
Common hazard	"Dread" hazard
Affects average people	Affects especially sensitive people
Will be used as intended	Likely to be misused
Consequences reversible	Consequences irreversible

*Generally, individuals make decisions on risks characterized by the descriptions on the left side of the table; a role for government intervention is often deemed more appropriate for those risks described on the right.

The government may also assume responsibility for informing consumers about the risks or hazards of products sold on the market if the seller does not provide adequate information. 9/ The government may provide the information to the consumer directly, or may require that the seller provide the information by means of product labelling. The objective in either case is to assist the consumer in making informed choices.

Simple provision of information may not guarantee that consumers will make appropriate decisions. For example, children, the illiterate, and those from non-English speaking backgrounds may not be able to read or understand the information that is being provided. There are also technical risks that cannot be easily conveyed to technically unsophisticated segments of the population.

A governmental role may be the consequence of the limited perspective of the individual. Many individuals have difficulty in assessing very small risks, 10/ which is important if the risks lead to very serious events such as death or disability. Individuals have difficulty relating future risks to the current use of a product; it is difficult to take into account risks that may not be realized for many years. Generally, individuals put lower values on events in the distant future than does society. 11/ Some individuals, even with the best information available to them, will disregard the risks either carelessly or willfully. 12/ In each of these cases government intervention comes into consideration, in part because the individual may require increased public expenditures, for instance on health care programs.

Policies that may restrict individual decision-making must recognize the existence of differential risks and benefits in the population. Some individuals may have smaller than average risks, others may derive larger than average benefits. An approach for dealing with segments of the population that face different risks would encompass attempts to restrain consumption of a product by those who will face high risks and small benefits while allowing easier access for those with low risks and large benefits. Although it is not always easy to identify the subject populations nor to design implementations that will produce the desired differential effects, a systematic approach to identifying those at risk and those who benefit can lead toward policies yielding the largest aggregate benefit.

A Decision Framework for Food Safety Policies

Some complex problems may be simplified if the required decisions can be structured in a sequential and hierarchical manner. As an illustration of a decision framework, consider a simple transportation problem. A person wishes to travel from the airport into the city and has the alternatives of taking a subway or taxi. The taxi is more convenient, since it offers door-to-door service, but poses a risk of being slowed by traffic congestion. The subway is faster, but also entails a walk of several blocks from the subway stop in town to the traveler's destination. The traveler knows enough about local traffic conditions to judge the probability and severity of traffic delays.* The decision-making process can be represented by the diagram shown in Figure 4-1. An ellipse represents the problem to be evaluated; a rectangle represents the information required to make the decision; a diamond represents a decision to be made; and a circle represents the outcome of the decision. In order to decide how to get from the airport to town, the individual makes use of knowledge of the risk (the likelihood of being delayed in traffic) and decides whether to accept that risk. Is the risk of traffic delay in a taxi made acceptable by the benefits of taking a taxi, such as door-to-door

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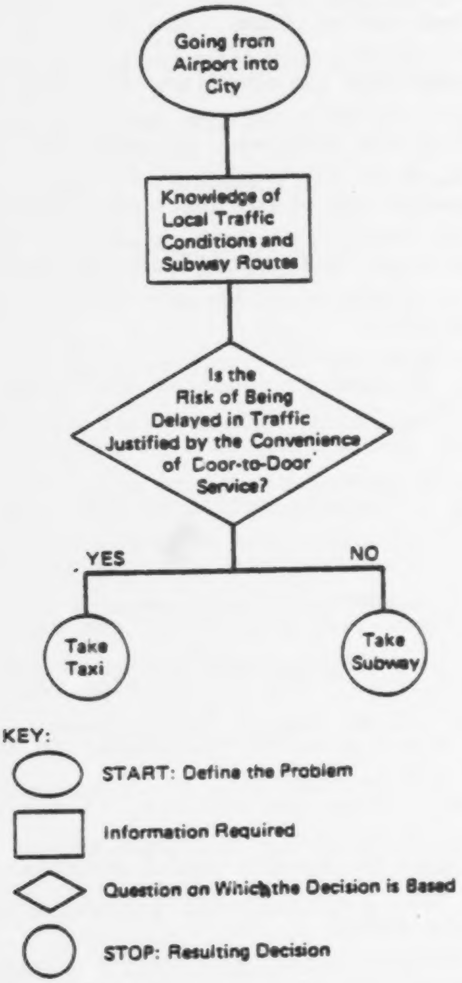
*The cost differences between the taxi ride and the subway ride are ignored for the sake of simplicity. This situation might apply if the individual is on an expense account.

Figure 4-1. An example of a decision framework.


Going from Airport into City
Knowledge of Local Traffic Conditions and Subway Routes
Is the Risk of Being Delayed in Traffic Justified by the Convenience of Door-to-Door Service?
YES
NO
Take Taxi
Take Subway
KEY:
START: Define the Problem
Information Required
Question on Which the Decision is Based
STOP: Resulting Decision

service? The answer depends on the individual's preferences, the consequences of being late, the weather, the packages to be carried, etc.

A decision framework indicates a logical structuring of the decision problem. It indicates the options available to the decision maker and the steps required to achieve the desired outcome, in our example, a balance between convenience and travel time. The decision framework helps to ensure that the assumptions involved are explicit and it provides an overall system for analyzing the problem. In addition, it identifies areas where information is needed and where there are uncertainties. It does not pretend to introduce rigor and quantification where concepts and data are inherently subjective.

A decision framework can be used to consider the risks and benefits of a food additive, along with the net benefits of regulating the use of that additive. The framework for making decisions can help to structure the problem and prevent decision makers from ignoring any of its important attributes. Although the ultimate subjectivity of the decision--"do the benefits justify accepting the risks?"--is not eliminated, the decision framework makes explicit the basis on which the answer is determined. It should be recognized, however, that the ordering of the relevant questions is in itself a decision that must be given careful consideration. This framework provides one possible order.

Let us consider a decision framework for evaluating the safety of a food additive (call it A) in a specific type of use. The relevant questions to the decision-maker might be:

1. Do health risks exist for food additive (A)?

2. Is there a less risky substitute for additive (A)?
3. If so, is the substitute significantly more expensive?
4. Do the health risks of the food additive (A) justify requiring use of the more expensive substitute?

If there is no less risky, acceptably priced substitute for (A), we should examine the severity of the risks and magnitude of benefits. It may be possible to permit consumption of the additive by those who are not likely to experience serious harm, and by those who reap high benefits.

5. Are the risks of consuming (A) diffusely spread over all consumers, or is it known that the risks are concentrated in identifiable groups of consumers?
6. If risk is concentrated, do the high-risk or low-risk consumers realize benefits that justify accepting the risks?

If there are risks to the entire consuming population, we may wish to consider separately the health and nonhealth benefits. We also should recognize that this framework considers health benefits first and then nonhealth benefits, including psychological and economic benefits.

7. For widespread risks, do the health benefits justify accepting the risks from consumption of additive (A)?
8. Do the health benefits and other benefits, taken together, justify accepting the risk from (A)? (The benefits need not be translated into commensurate units for this analysis.)*

The major steps of the food additive decision process are illustrated in Figure 4-2. 13,14,15/ The steps are identified alphabetically for

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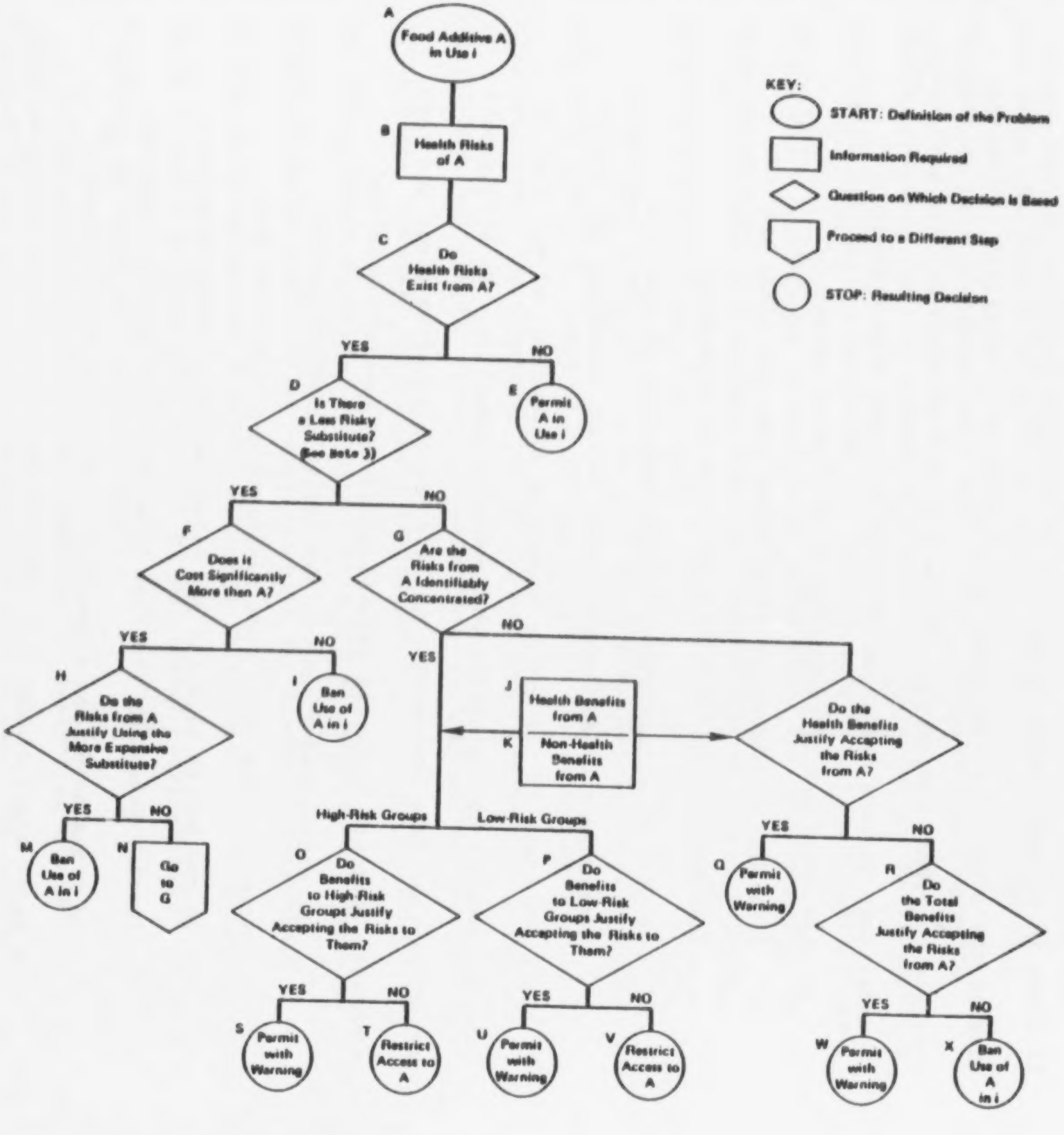
*For a discussion of such measurement issues see, 16,17,18,19,20/

Figure 4-2. An illustration of a decision process for food additives.


A
Food Additive A in Use i
B
Health Risks of A
C
Do Health Risks Exist from A?
YES
NO
D
Is There a Less Risky Substitute? (See Note 3)
E
Permit A in Use i
YES
NO
F
Does it Cost Significantly More than A?
G
Are the Risks from A Identifiably Concentrated?
YES
NO
H
Do the Risks from A Justify Using the More Expensive Substitute?
I
Ban Use of A in i
YES
NO
M
Ban Use of A in i
N
Go to G
YES
NO
J
Health Benefits from A
K
Non-Health Benefits from A
High-Risk Groups
Low-Risk Groups
O
Do Benefits to High-Risk Groups Justify Accepting the Risks to Them?
P
Do Benefits to Low-Risk Groups Justify Accepting the Risks to Them?
YES
NO
S
Permit with Warning
T
Restrict Access to A
U
Permit with Warning
V
Restrict Access to A
Do the Health Benefits Justify Accepting the Risks from A?
YES
NO
Q
Permit with Warning
R
Do the Total Benefits Justify Accepting the Risks from A?
YES
NO
W
Permit with Warning
X
Ban Use of A in i
KEY:
START: Definition of the Problem
Information Required
Question on Which Decision Is Based
Proceed to a Different Step
STOP: Resulting Decision

NOTES FOR FIGURE 4-2

1. An ellipse represents the starting point of the analysis. Rectangles represent informational inputs to the decision process. In this example, the required information is the scientific or technical evidence on the existence, magnitude, and distribution of the health risks; the health benefits; and the nonhealth benefits, attributable to the consumption of the additive in a specific use. Diamonds represent decisions from which the subsequent path is determined by the answer to the question. Pentagons represent instructions to go to a different step in the decision-making process, and circles represent end points indicating the appropriate regulatory policy.

2. This illustration can be expanded and modified. For example, the consideration of risk groups at O and P can be expanded to include three or more categories.

3. Benefits are an integral part of the concept of a substitute. The term substitute, as used in D, F, and H, refers to a substance essentially similar to the additive (A) in all relevent properties except risk and cost.

4. This decision process can be modified to apply to foods with contaminants, naturally-occurring toxic substances, etc.

reference in the discussion that follows. Each distinctive step in the decision framework is identified by a symbol of a different shape as shown by the key.

The food additive decision process in Figure 4-2 outlines the sequential evaluations required to arrive at a policy decision. It begins with consideration of a food additive (A) in a specific use i, based on the assumptions that one may desire alternative policies for controlling the food additive in distinguishable uses, and that enough is known about the health effects in different uses to make such a distinction feasible in the decision process.

Three kinds of information are required as inputs: a scientific assessment of the magnitude and distribution of the health risks resulting from consumption of the food additive (A) in use i in step (B); the health benefits attributable to its consumption in step (J); and any nonhealth benefits attributable to its consumption in step (K). It should be noted that the uses differ not only in the quantity of additive (A) consumed, but also in other characteristics. For example, saccharin may be considered as a consumer-added sweetener, as a substance in soda, and as a substance in toothpaste.*

If insufficient information prevents at the time of the policy evaluation a conclusive decision, it may have to be postponed. This in itself is an important decision, and can result in implementation of a temporary policy until the required information becomes available.

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*Appendix E illustrates the use of this decision framework as it applies to saccharin.

Depending on the circumstances of substitute availability and whether the risks and benefits are concentrated in identifiable population groups, the question of risk acceptability can be raised in four ways:

1. If a more expensive, but less risky, substitute for additive (A) is available, is the higher cost justified by the reduction in risks (H in Figure 4-2)?
2. If there is not a less risky substitute at acceptable cost and the risks from consumption of (A) are concentrated in identifiable population groups, do these groups also realize benefits from consumption that justify acceptance of the risks (O and P)?
3. If there is no acceptable substitute and the health risks are spread diffusely over the population, do the health benefits from consuming (A) justify acceptance of the risks (L)?
4. From question 3 above, if the health benefits alone do not justify accepting the risks, does the combination of health and nonhealth benefits justify the risks (R)?

The decision framework is suitable for use both with a "risk-averse" and a "risk neutral" attitude on the part of society or its policymakers. The four possible risk-acceptability judgments mentioned above can be made according to criteria that are risk-averse: "If the risk is cancer, no possible benefits justify the risk." Other decision-makers may adopt a different position: "When estimated in commensurate terms, do the expected aggregate benefits exceed the expected aggregate harmful effects attributable to consumption of the additive?"* The decision framework does not embody the criteria by which a risk is judged acceptable nor does it obviate a subjective judgment.

This framework could be extensively modified or expanded. A more complex decision process could be designed to allow for high, medium, and low-risk (and benefit) categories of populations. Similarly, frameworks could be designed to evaluate groups of substitutes, each of which may pose a different risk.

The principal attributes of the decision framework which make it a useful tool are:

1. It separates aggregate uses of an additive into specific uses and facilitates a policy with respect to each use.
2. It enables the classification of users into high-risk and low-risk groups and high-benefit and low-benefit groups, and leads to a policy decision with respect to each group.
3. It takes into account the availability or absence of technological substitutes for the additive, and considers their costs.
4. It expressly calls attention to the possibility of health benefits.

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*For a discussion and critique of risk-benefit and cost-benefit analysis see Acton, 18/ Schelling, 10/ and Zeckhauser. 20/

5. It entails the consideration of nonhealth benefits in circumstances where these may be significant, and allows differential weighting of health and nonhealth effects.

A discriminating policy for each of several uses of a food additive can be complex in its implementation. Several methods to deter or restrict access may be required, including educational programs, warning labels, legal barriers, or taxation. The alternatives must be evaluated for effectiveness, the distribution of risks, and associated costs. Situations could arise where the entire population benefited from removal of a risk, but only a small part of the population bore the additional cost.

The decision framework as presented omits some important considerations. Policy questions cannot always be answered on a "yes-no" basis because of the complexity of the questions being addressed. The results might be a qualified "yes" or "no" or a probabilistic "maybe." There are also differences between a decision to prohibit marketing of a new food additive 21/ and a decision to remove one from the market after it has achieved widespread use and acceptance. The social costs of banning an existing product are different in the two instances, not only because of administrative and enforcement costs, but also because producers and consumers may experience a loss from the additive's removal. The costs of the policy decision also can include the dislocation of an industry while its plant, equipment, and labor are redirected or employed in alternative uses. Although these "transition costs" are low for many food additives, in those cases where these costs are demonstrably large, they should be appropriately recognized in the policy decision.

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Chapter 5

TECHNIQUES FOR THE ASSESSMENT OF HEALTH RISKS*

Health Risks from Food Substances

Harmful health effects from food substances range from mild temporary allergic reactions to debilitating illness to premature death. Present methods are generally adequate for detecting causes of acute effects that appear soon after exposure, and which are often reversible after the chemical or other cause is removed. Therefore, the current research emphasis is on preventing progressive, chronic diseases with long latent periods, such as cancer, where the problem may appear or persist long after initial exposure to causative agents.

Diet in general, or particular substances in foods, may be causative factors in many human health problems--cardiovascular diseases, cancer, congenital malformations, behavioral and central nervous system disorders, and others. 1/ This chapter will emphasize the detection of potential mutagens and carcinogens in food.

Major factors that determine health risk from food include: the intrinsic nature of the chemical, which is independent of whether it occurs naturally or is added in food production or preparation; the susceptibility of a person to the substance; and the type and extent of exposure, which depends on the quantity of material present and the time over which exposure occurs, in other words, the "dose." 2/

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*Chapter 6 describes some techniques for assessing health benefits, including a brief description of clinical trials. Many of the same techniques and problems apply to assessing health risks and health benefits. Surveillance techniques for assessing health risks are discussed in greater detail in Chapter 7.

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Various food substances could theoretically be assigned to broad risk categories such as high, moderate, and low risk based upon consideration of the health effect, exposure dose, size and susceptibility of the exposed population, and possibly other factors. After considering all these factors, some substances or foods would represent a higher risk than others, but judgment would be required in assigning substances to specific categories, and in setting regulatory priorities. Substances to which many people are exposed may represent a greater potential health risk to society than substances to which only a small group is exposed. Irreversible or potentially fatal effects would be weighted more heavily than mild temporary effects. Chapter 9 considers the necessity of categorizing risks in order to set regulatory policy and determine priorities for action, because it would be impossible to explicitly test and regulate every substance found in food.

Any substance is likely to be harmful in excessive quantities, but the same substance that produces ill effects in large quantities may be harmless, or even necessary, in lesser amounts. Nutrients such as vitamins A and D, salt, and fats are in this category.

For some diseases or substances, the effect may appear only after continuous exposure to low levels of a toxic substance, or long after one or a few exposures to larger quantities. Ingesting a substance may be more or less harmful than exposure through skin or lungs. The development and progress of some diseases, such as cancer, occur in several stages which may be differentially sensitive to environmental substances. People have varying susceptibility to harmful agents; small amounts of some substances may harm genetically susceptible individuals, or fetuses, children, the elderly, or those already weakened for other reasons, whereas much larger quantities may have no effect on more resistant individuals.

Since people do not live in a well-controlled environment, they are exposed to many potentially hazardous substances. This situation causes uncertainties in assessing health risks because relatively little is known about the effects of adding a small additional risk to an environment already replete with risk factors. Most government regulations treat each substance separately in setting acceptable exposure levels. Food, however, is only one of the ways in which people are exposed to potentially hazardous substances. This problem is compounded by the possibility that risk factors may interact synergistically or antagonistically to produce a much greater, or lesser, health effect than would be predicted if the risks from all factors were considered to act independently. Such interaction is of particular importance for cancer, where exposure to very low levels of many carcinogens may lead to substantial risk of disease.

In discussing health effects, people often consider carcinogenesis, mutagenesis, and teratogenesis together, in part because they are irreversible and analyses of these processes share many methodologic procedures and problems. Mutagenesis and carcinogenesis are probably closely related, since evidence suggests that most cancers begin with a mutational event. 3,4/ However, environmental teratogenesis (production of birth defects) occurs by several different molecular mechanisms, 5/ only some of which overlap with carcinogenic action. Teratogens typically interfere with the function of many cells and disrupt the orderly stepwise development of a fetus. Their effects often depend not only on dose but also on the precise period during gestation when exposure occurred.

Cancers whose etiology involves environmental factors--and these may be the majority--are thought to develop via a multistep mechanism. 3,4/ A positive association between exposure and the occurrence of cancer in humans has been observed for about 30 chemicals, activities, or industrial processes. 6/ For another 200 chemicals that are carcinogenic in at least one animal species, definitive evidence is lacking to show that exposure induces human cancers. 6/ Even with the most active carcinogenic chemicals, the process of cancer development is slow, usually requiring the equivalent of one-quarter to one-half of the species' average lifetime. Cancer development begins with initiation (possibly synonymous with mutation in one of the body's cells). During the subsequent period of apparent latency, the "initiated" cell may be undergoing multistep changes, ultimately to become a malignant cell. However, for the process to culminate in a cancer cell, "promotion" appears to be essential. The initiation event apparently is irreversible, but many of the events that occur during promotion and before appearance of a cancer seem to be reversible. Thus, for carcinogenesis by many chemicals, continual exposure to a promoting environment over a relatively long period increases the likelihood of development of cancer. But the essential nature of the promotion process is not yet understood.

Most carcinogenic agents are active only after metabolic coversion to highly reactive compounds that are "electrophilic" (electron seeking). These active chemicals can interact with many different cell constituents, but their effects on the cell's genetic material, DNA, are believed to have special relevance to the initiation of cancer. In some instances, DNA repair processes may play an important role in modulating the initiation events produced by carcinogens. 7/

Diet may be important in cancer etiology in at least two ways: 1) as a vehicle for compounds or agents that can initiate or promote the cancer development, and 2) as a modulating influence in increasing or decreasing the metabolic generation of potentially toxic agents originating elsewhere in the environment or within the body.

Overview of Methods for Detecting Health Hazards

Measurement and quantification (or at least ranking) of risks to human health are required for risk and benefit assessment. (See Chapter 4 for a general discussion). Assessment of risk to health depends on data obtained from three general kinds of investigations: 1) epidemiologic studies of disease occurrence and distribution in populations 2) animal experiments, and 3) short-term tests* on bacteria, cultured mammalian cells, or other biological systems. Each of these methods has advantages and limitations.

Epidemiologic and related clinical studies observe human populations, and are useful in studying a broad range of health effects. 8/ Since epidemiologic studies are often observational rather than experimental in nature, they have practical problems that may limit their usefulness. For example, they provide relevant information only when the substance in question has a relatively large effect and is already in use; other methods must be relied upon to provide data on new substances, or on known substances to be used in new ways.

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*Short-term tests" in this report are the wide variety of tests designed to detect mutagens and carcinogens by determining whether a substance produces gene damage, chromosome damage, or cell transformation. These tests generally take a few days to a few months.

Experimental animal studies are now the most commonly used method of detecting harmful effects of a substance, including acute effects, possible teratogenic or carcinogenic effects, or effects on specific organs. These experiments can be carried out under controlled conditions, and various procedures exist for attempting to relate the effects observed in animals to potential effects in humans.

Short-term tests are the newest method of determining the ability of substances to cause gene damage, including mutations and chromosome aberrations, or to induce transformation in isolated cells. Many compounds that are carcinogenic in animals also are positive in short-term tests, but some carcinogens that are positive in animal studies do not show mutagenic activity in short-term tests. 9-12/ A number of these tests are well developed and in current use. Research is continuing in this rapidly moving field in order to provide rapid screening methods to identify potential carcinogens and mutagens, to increase understanding of the tests' capabilities and limitations, and to determine optimum procedures for carrying out the various tests.

EPIDEMIOLOGY

Epidemiologic studies can help in quantifying the relationship between exposure to a substance or agent and the occurrence of disease in human beings. The goal is to identify and if possible, quantify causal relationships. The assessment of health risk is accomplished by comparing the proportion of diseased individuals in different groups known to have had differing levels of exposure, including no exposure. The choice of the unexposed group is often crucial for obtaining useful information. Difficulties in epidemiologic assessment of risks from foods are caused by the diversity of the food supply, the diversity of patterns of consumption, and the presence of many possible "confounding factors.*

Epidemiologic studies can be observational or can be more experimental in nature. Epidemiologists generally must take circumstances as they are, rather than performing experiments designed to provide more easily interpreted data, as is possible in studies with laboratory animals. However, sometimes experiments with humans may be carried out. Moreover, careful selection and analysis of sample populations can increase the usefulness of observational data as well as experimental data. A brief discussion of some basic methods that epidemiologist use in collecting and interpreting information will aid in understanding the power and limits of this field in assessing health risks.

Approaches

Generation of Epidemiologic Hypotheses

The recognition of a risk to human health often begins with the judicious observation (usually by a clinician) of an unexpected clustering of cases of a disease with some unusual exposure component in common. Scrotal cancer seen in chimney sweeps 200 years ago is a classic example of such clinical observation. More recently, clinicans recognized an increase in cataracts in children exposed to rubella in utero. 14/ Another example is the observation of three cases of angiosarcoma of the liver in a group of people who worked in the same area of a chemical plant where they were exposed to vinyl chloride. 15/ Subsequent epidemiologic studies supported the causal relationships suggested by these original observations.

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*A confounding factor is a factor that contributes to a disease incidence, and to which exposure frequently occurs under the same conditions as exposure to a substance whose effects are being studied. An incorrect estimate of the risk due to the substance being studied will be made if confounding factors are present but ignored. For example it might be concluded that an inexpensive food item is a risk factor for a disease. However, if that food were eaten primarily by poorer people, then a condition associated with poverty might contribute to the disease incidence. Such a condition would be a confounding factor in the study, because the disease actually would be entirely or partly due to the condition rather than to the food item itself. 13/

To generate hypotheses that associate diet with disease, epidemiologists may look at the distribution of specific diseases in populations or at special circumstances of exposure. These studies commonly involve systematic searches for variation of disease frequency with age, sex, race, and other demographic variables. Diet patterns may or may not be included in such systematic surveys. Studies of disease rates in migrants* are useful since large changes in dietary patterns may occur, but other environmental changes need to be taken into account. Also of interest are the health and disease patterns of population groups with special exposures, such as vegetarians, or religious groups that follow special dietary rules.

Testing Hypotheses

Hypotheses generated by earlier epidemiologic studies, clinical observations, or animal studies must be further tested by controlled observations on individuals or observations on larger numbers of individuals than initially noted. For example, if a study of two populations with different smoking habits suggests that smoking increases lung cancer risk, an increased disease incidence should be seen when identified smokers are compared with non-smokers. Other possible explanations for the increased lung cancer among smokers would need to be taken into account.

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*Migrants, in this context, are ethnic or other groups who no longer live in their native land. Japanese in Japan have a higher incidence of stomach cancer than is found in the U.S. However, when Japanese move to the U.S., their cancer incidence approaches that found in the host country, suggesting that some environmental factor or factors are important. 3/

Studies of individuals may take the form either of prospective cohort studies or of retrospective case-control studies. Cohort studies identify groups of healthy individuals with known exposure or lack of exposure to particular food substances, for example, and follow these individuals to determine the incidence of suspect food-induced disease. Case-control studies identify individuals with the suspect disease, and seek to determine their prior consumption of the potentially harmful food substance. Both kinds of studies require control groups that differ as little as possible from the exposed or diseased persons except for the particular variable being tested, (i.e., the disease status or the prior exposure). Establishing suitable controls is one of the more difficult tasks of epidemiology.

Seldom is it ethically or morally possible to confirm etiologic hypotheses experimentally in human subjects. Exceptions include acute reversible effects, such as the syndrome induced by monosodium glutamate (MSG), 16/ and prophylactic trials, which test preventive measures in a selected population at risk. An example of the latter is the

Multiple Risk Factor Intervention Trial (MRFIT), which tests the effects of simultaneous modification of various risk factors for coronary heart disease in a group of people. 17/ The rate of coronary heart disease in the intervention group is compared with the rate in a similar control group who obtained their doctor's usual care.

Study of Special Populations

Population groups characterized by unusual exposure or unusual susceptibility may have large disease risks, which reduce the problems of sample size and confounding factors for the epidemiologist. For instance, one could conceive that persons occupationally exposed to large quantities of particular food substances (as in production or processing plants) may exhibit disease rates many-fold greater than those seen in consumers of the food, and look for such effects. Diabetic patients have been studied extensively as a group with an unusually heavy use of non-nutritive sweeteners. 18/ Studies of the effects of various factors on the health of susceptible members of a population, such as fetuses, children, and the elderly, may aid in understanding the range of susceptibility for various diseases, and may provide information necessary for protecting these groups.

Studies of special populations, however, have their limitations of interpretation. Occupational exposure to a food substance can involve routes of entry other than ingestion and thus may have little relevance to the possible effects of consuming foods. Exposures at concentrations many-fold greater than those commonly involved in food consumption may invoke different biochemical mechanisms of activation or detoxification so that extrapolation to low dose effects may be invalid. Effects seen in populations with special susceptibility, high or low, may be unique to these populations and have little or no generalizability. It has been suggested, for instance, that the absence of observable carcinogenic effect of saccharin in diabetic patients may be due to a lack of susceptibility associated with the diabetic state, and may not reflect saccharin's carcinogenic potential for the non-diabetic population.

Establishing Causality

Several types of bias may hamper the interpretation of epidemiologic studies: bias in selecting cases and controls; interviewer bias, particularly if the interviewer knows the case or control status of the subject; errors in diagnosis of disease; recall bias because cases may remember their experience with greater clarity than controls (a definite problem in studies of chronic diseases and the use of specific foods); and, when exposure cannot be measured directly, inappropriate use of indirect exposure estimates, such as national statistics on per capita consumption of foods.

In the face of possible bias, epidemiologists establish causality by fulfilling as many as possible of the following criteria: 19/

1. Strength of association. The greater the correlation between the presence of the factor under study and the presence of disease, the more likely that the relationship is causal and not attributable to known or unknown confounding factors.

2. Confirmation of the study. Confirmation of a study's findings by other researchers decreases the chance that the association is an artifact.

3. Biological plausibility. Are the effects in human beings consistent with animal experiments or other biological data? Relevant information is often not available for food substances suspected of causing chronic disease.

4. Temporal sequence. Because cause must precede effect, studies that record exposure and disease status without regard to which came first may be less reliable for inferring causal relationships than case-control and cohort studies that have a clear time frame.

5. Dose-response gradient. The finding of increased incidence of disease with increasing exposure to the substance in question suggests a biologic interaction. When the cause is removed, the effect should diminish or disappear.

Limitation of Epidemiologic Studies

In determining effects of food substances, traditional clinical and epidemiologic methods are generally adequate for studying acute, reversible effects. Difficulties arise, however, in correlating food consumption with progressive diseases that are associated with long latent periods and long exposure times. Such studies require large populations, adequate exposure data, and careful analysis of confounding factors.

Long latent period and exposure time Food substances newly introduced to the market may cause adverse effects, such as behavioral abnormalities, cancer, or hypertension, that are not detected until many years later. If a food substance is suspected of causing delayed adverse effects, epidemiologists have the difficult task of finding previous consumers of the substance, and then following them for many more years to determine the possible health consequences. Another reason that adverse effects go unrecognized for a long time is that some substances cause harm only after long-term exposure.

Moreover, there may be uncertainty about actual exposure because a substance may remain in cells beyond the period of known exposure. For example, saccharin is quickly excreted, 18/ but other substances may be retained for weeks or months after introduction into the body ceases.

Need for large populations The relative increase in risk due to food substances is usually much less than a doubling and often is only a small fraction of the background risk from causes other than the food under study. In seeking small effects, large populations are required to assure adequate numbers of cases in cohort studies so that any effects will be visible above the background.

Limitations of consumption data Food substances are so widely distributed that population groups with special exposure or absence of exposure may be difficult or impossible to identify. Studies related to changes in the amounts of specific substances in the food supply with time may sometimes suggest disease patterns, but studies of groups cannot relate exposure to health effects in individuals. Uncertainty arises in studying individuals because they not only have difficulty recalling foods eaten in the past, but generally have only limited information about additives they eat and virtually no information about contaminants.

Confounding variables For the small, relative increases in risk generally associated with individual food substances, unknown confounding variables may obscure causal associations or create spurious associations. Furthermore, small effects taken in aggregate may lead to significant total effects that cannot be attributed to any single agent. The possibility of unsuspected confounding variables is usually the principal reason for uncertainty in interpreting epidemiologic data.

Many of the problems enumerated above can, in theory, be solved by using sufficiently large populations and sensitive survey techniques, but in practice it may not always be possible to eliminate the inherent problems. Sampling a large enough population is one such practical consideration.

It is possible to calculate the size of the sample needed in order to have a reasonable chance, say 80 percent, of finding an effect such as an increased risk of disease due to consumption of a particular food. 22/ In case-control (retrospective) epidemiologic studies, the number of people who must be studied depends on the frequency with which the population is exposed to the substance. For instance, if one person in ten on the average is exposed, then when testing at the 0.05

statistical significance level, the study would need approximately 200 people with the disease and 200 healthy people (controls) in order to detect a doubling in the risk for the disease. As the average frequency of exposure to the chemical decreases, then the size of the population that must be studied increases. If exposure is, on the average, one in one thousand, then 18,000 cases of the disease and 18,000 healthy people should be included in the study. The number of people recruited into a study must increase if the magnitude of the anticipated effect is smaller than the doubling stipulated in the previous calculation . The number of people can decrease if the effect is larger than a doubling.

Several other factors contribute to the ease or difficulty of assembling a large enough study population. If a condition is rare, it may be relatively easy to identify but it will be extremely difficult to find appropriate cases. The incidence of some cancers, for instance is less than 20,000 cases per year. The subtleties of expression of some diseases, such as behaviorial disorders, also make it difficult to identify cases, even though they are relatively common.

The length of the latent period between exposure to a substance and expression of disease also must be considered when designing epidemiologic studies. If a long latent period is anticipated, then the sample population must be larger than if there is a negligible latent period. Not only do confounding factors accumulate during the latent period, but participants in the study drop out and are not available at the termination of the study period.

Even if sufficient resources were available to carry out large epidemiologic studies, factors other than the suspect food substance and the health effect of interest still must be taken into account. Statistical correction for known confounding factors can sometimes be effective. However, unsuspected confounding factors can best be controlled through experimental investigation, but possibilities for human experimentation are limited by ethical and other considerations.

Because of the problems already noted, as well as the time-consuming and expensive nature of many epidemiologic studies, they can rarely provide ready answers to current regulatory questions. For example, few data are available to show the unintended effects,either harmful or beneficial,that might occur if the availability of saccharin and foods containing saccharin changed. As noted in Chapter 7, increased surveillance and research are required to obtain data that regulators can use in making decisions, and to monitor the effects of regulations.

Interpreting Epidemiologic Studies

Despite the difficulties in establishing causality and the limitations of epidemiologic methods, in cases where valid epidemiologic data exist, they provide the best evidence to support an association between exposure to a substance and development of a particular human disease. 23/ Epidemiologic methods are generally insensitive for detecting relatively small changes in disease occurrence. If a new ingredient in a common food caused a 10 percent increase in cancers of the colon and rectum 20 years after its introducton, the cause might never be noted, although about 5,000 extra deaths would occur annually in the U.S. (based on 1976 mortality data). 20/

Because of this methodologic insensitivity, a negative finding in even a well-conducted epidemiologic study does not eliminate the possibility of an important hazard. In fact, the report of a negative epidemiologic finding is incomplete without a statement of the minimum risk that could have been detected, given experimental limitations. An analysis of this kind would reduce the confusion that often develops when a substance appears to be a carcinogen in animal tests but not in human epidemiologic studies.

Similarly, many of the same methodologic problems may lead to positive findings when no true hazard is present. Therefore, reports of positive findings should be accompanied by a statement of the least positive result that can reasonably be accepted as indicating a true effect. Increases in risk of less than three-fold are generally not considered "strong" associations and may reflect associations with confounding variables.

ANIMAL TESTS

Aspects of Methods

Rationale for Using Animals

There are basic similarities between lower animals and human beings in the way their cells and tissues respond to toxic or hazardous agents.

Well-conducted animal experiments, notwithstanding quantitative variation among species, are important in evaluating potential health risk to humans, particularly of proposed new food constituents.

Animal studies enable toxicity testing under controlled experimental conditions and most suitable choice of species, dose, and the method of administering a substance. A wide range of health effects can be studied, ranging from acute toxicity to long-term effects such as cancer expression or effects in offspring. Effects can be followed over time by sacrificing the animals at intervals and examining organs and tissues anatomically, pathologically, or biochemically. However, precautions must be taken in quantitatively extrapolating results in animals to potential health effects in humans.

A recent report states the rationale for using animals in testing carcinogens.

> Animal tests are the best current method for predicting the carcinogenic effect of substances in humans. All substances demonstrated to be carcinogenic in animals are regarded as potential human carcinogens; no clear distinctions exist between those that cause cancer in laboratory animals and those that cause it in humans. The empirical evidence overwhelmingly supports this hypothesis. 24/

Similar reasoning applies to detecting causes of other health problems with long latent periods.

Choice of Animal Species

The best theoretical animal model is not necessarily the best practical one. The best theoretical model would be the species most similar to human beings in its response to the substance under consideration. But to detect carcinogens or other toxic substances that show effects at low incidence and only after long latent periods, the best experiments would involve hundreds of thousands of animals, exposed to substances at the same level and by the same route of administration as encountered by humans. Some testing guidelines would also require that the animals be followed for at least two generations in order to detect a carcinogenic effect. The best practical model is to use small animals, which have lifetimes of two to three years.

Additional practical considerations, such as the cost of purchasing and maintaining animals, dominate the choice of test species. Mice and rats are almost invariably used in experiments that extend over long periods of time. The rationale for use of rodents is clear when one considers a common protocol for testing potentially carcinogenic substances. It requires testing two animal species, using 50 animals of each sex at two dosage levels for each species, for a minimum of 300 animals per species per experiment including the 100 untreated controls. 25/ Even with small rodents, a two-species test may exceed $500,000 in cost and take up to three years. Because of practical limitations, only a limited number of substances can undergo this extensive testing.

In choosing the species for testing, biochemical and metabolic considerations also must be taken into account. Mammals metabolize most of the compounds they ingest into products that may be either more or less toxic than the original substance. Despite general metabolic similarity, however, individual species exhibit differences in the way they metabolize substances. In choosing appropriate species for testing a particular toxic substance, the results will more readily apply to humans if the animal model metabolizes the compound by pathways similar to those found in humans. In addition, the more animal species that are used, the greater the chance that one or more of them will reveal a substance's potentially adverse effects.

Dose of Substance and Route of Entry

Researchers usually consider an effect statistically significant if it would occur by chance no more than five percent of the time. Even if no response occurs among 100 animals, it is only possible to conclude (with 95 percent confidence) that the true frequency of disease induction at the given dose is less than three percent. A likelihood of inducing a disease in no more than 3 out of 100 humans represents six million cases a year in the U.S. Even an annual disease incidence of 0.01 percent in a human population would be considered a disaster in the U.S., where it would represent about 20,000 cases per year.

High doses increase the percentage of exposed animals that will show deleterious health effects and provide a way of compensating for the practical inability to use more than a few hundred animals in most tests. High doses also may decrease the latent period for appearance of effects. Since human exposures usually occur at much lower doses, the applicability of results obtained with the high doses used in animal studies frequently have been challenged. However, if the doses used do not otherwise affect longevity or survival, or produce other toxicity, the results in regard to inducing a particular toxic effect are generally considered valid, particularly if a dose-response correlation is demonstrated and the experiments follow established guidelines. 25,26/

In testing the potential toxic effects of a substance, animals ideally should receive the compound by the same route that humans do. Thus, ingestion is the most appropriate route for testing food substances, but problems such as low palatability or other effects may sometimes necessitate alternate routes.

Estimating Human Risk

Extrapolation from Animals to Human Beings

For many classical toxicologic responses, such as changes in organ weight, inhibition of enzyme systems, sensory irritation, and decrease in fertility, dose-response curves show that some minimum level of exposure is necessary to produce the response. Below this exposure level, called a threshold, there are no observable effects because natural physiologic mechanisms can detoxify the substance, eliminate it, repair its damage, or otherwise prevent its action. 26/ For compounds that show such a threshold in animals, a level of acceptable exposure for humans is normally set that incorporates a safety factor. The magnitude of the safety factor, ranging from 10 to 5,000 in practice, depends on the toxic effects produced, the slope of the dose-response curve, the quality of data, and other variables. The general practice for establishing permissible levels of food additives has been to use a safety factor of 100. 27/

A major question about carcinogens is whether substances carcinogenic at high doses in animals are carcinogenic in animals or humans at low doses. Practical problems of sample size prevent measurement of low dose effects If thresholds do exist for carcinogens, many researchers agree that it is statistically impossible at present to prove it.

For compounds that are actual or suspected carcinogens, various mathematical models have been devised to allow use of results from experimental animal bioassays conducted at high doses to estimate effects at lower exposure levels. These mathematical models are discussed in some detail in Part 1 of this report, 18/ and the appropriate section is reproduced as Appendix F. The practical difficulties with application of this high dose extrapolation methodology are: 1) most models appear similar to one another in the range of dose levels that produce measurable responses, yet may be considerably different when extrapolating far below this range; and 2) for any model that adequately describes the experimental results in the high dose-range, there is no guarantee that it necessarily describes the expected results at substantially lower dose levels.*

The extrapolated animal data from any model must still be converted to an estimate of possible risk in humans. Uncertainty about carcinogenic mechanisms makes it impossible to use animal data to estimate with confidence the degree of human risk. The following differences may complicate attempts to use animal data to estimate potential human health risk. 28/

1. Laboratory animal populations used in testing are usually highly inbred, so that all individuals of a population are genetically almost identical. Their response to a chemical would be fairly uniform, but two different inbred populations might differ markedly in their response. Human populations, on the other hand, have a varied genetic makeup, so would show a wide range of responses to a chemical. In extrapolating from animals to humans the conservative assumption in favor of safety is that the average person is as sensitive as the most sensitive experimental animal species.

2. Human beings are exposed to many carcinogens on an irregular basis, whereas experimental animals are usually exposed to a single (known) carcinogen in a methodical way.

3. The effective exposure level, i.e., the amount of carcinogen actually reaching target cells, may be some complex function of absorption, distribution, metabolism, and excretion. Comparable metabolic

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* Regardless of these drawbacks, the mathematical models are generally considered to be less arbitrary than methods used previously to estimate risk at low doses.

information for the test species and humans is often not available. Primary target cells often differ among species. The question of whether to use body weight or surface area in scaling from animals to humans has never been fully resolved.

Comparing Animal and Human Data on Sensitivity to Carcinogens

Limited data exist that compare human and animal susceptibility to carcinogens. A National Academy of Sciences panel reviewed and compared available data for six substances for which human exposure and induced incidence could be at least roughly estimated: benzidine, chlornaphazine, diethylstilbestrol, aflatoxin B, vinyl chloride, and cigarette smoke. 29/ The carcinogens for which enough data were available for comparisons are those already identified as human carcinogens, so they may be the substances to which humans are most sensitive although other factors may introduce the opposite bias. The limited conclusion was that if the data from the most sensitive rodent tested are used to predict lifetime human incidence on a dose per body weight basis, the result was approximately correct for benzidine, chlornaphazine, and cigarette smoke, but human sensitivity was overestimated in the other three cases. As a conservative working hypothesis, the panel concluded that it seems reasonable to assume that the lifetime cancer incidence induced by chronic exposure in humans can be approximated by the lifetime incidence induced by similar exposure in laboratory animals, if calculated at the same total dose per body weight.

Interpreting Positive and Negative Results of Animal Tests

Positive results in test experimental animals, if obtained under sound experimental conditions and with proper statistical confirmation, should be given greater weight than negative results. This follows from a conservative approach to human safety and because laboratory bioassays conducted with limited numbers of animals, or a relatively insensitive animal species, can easily yield false negative results. However, sound negative studies may provide valuable information. If both positive and negative results have been obtained, an effort should be made to demonstrate the reason for the conflicting results before the testing process is regarded as completed. Useful new insights frequently result from such efforts.

In evaluating results, therefore, careful attention must be given to the quality of the experiments performed and to biologic and statistical criteria for a positive outcome. Biologic features of a positive outcome include appropriate dose-response and time-dose relationships and absence of signs that the doses employed induced toxicity other than the effect being studied. Where possible, similar studies using several different animal species should be evaluated. Conservative considerations of safety require that data from the most sensitive species be used for estimating human risk.

SHORT-TERM TESTS

Rationale

Short-term tests provide a relatively rapid and inexpensive means for screening compounds that may cause mutations, other kinds of genetic damage, or cell transformation. The tests are useful primarily for screening for mutagens and carcinogens.

There are many thousands of environmental and industrial chemicals that may be carcinogenic and it is impractical to test a large proportion of them using the kinds of animals tests just described. For this reason, short-term tests are attractive. Individual short-term tests on a compound generally vary in cost from a few hundred dollars to about $10,000, and take a few days to a few months to perform. 30/ These figures contrast with the $500,000 and several years required for the usual animal tests.

Most short-term tests used to forecast carcinogenicity are based on the presumption that one of the steps in the multistep development of cancer involves changes in DNA, and that a compound's ability to alter DNA may be correlated with its ability to cause cancer. Chromosome damage, mutagenesis, and other genetic effects seen in the bacteria or other cells employed for short-term tests reflect damage to DNA. Some of the cells used in short-term tests cannot by themselves convert the carcinogens or mutagens to active forms; in these cases a tissue extract or mammalian enzyme preparation is added to carry out the conversion. The active product(s) then interacts with sites in the test cells. Microorganisms often are used in the short-term tests, but in a few systems, mammalian cells are used. The latter can provide a more complex and perhaps more relevant end-point, "cellular transformation."

The main question about any test that does not directly measure appearance of the disease of concern is whether the test response is actually related to the disease. Various studies have attempted to correlate the ability of short-term tests to detect carcinogens already identified in animal studies, although there is often uncertainty in categorizing compounds as "non-carcinogens." 9-12/ Nonetheless, the Ames/Salmonella test, the transformation tests, and other short-term tests have been particularly effective in discriminating between carcinogens and non-carcinogens. Discrepancies seen among the experimental results of various researchers may reflect the lack of standardized procedures for carrying out some of the tests, 31-34/ because methods are steadily being improved. As examples, researchers may develop more sensitive strains of cells and may attempt to optimize the enzyme preparations that activate the test chemical.

Specific Tests

Current short-term tests involve a variety of biological systems including bacteria, yeast, fruit flies, cultured mammalian cells, and mammals for *in vivo* tests. The following description of selected short-term tests provides examples of the procedures. 4,35/

Mutagenic activity can be measured in bacteria such as Salmonella and Escherichia coli, or in higher organisms, such as yeast, the mold Neurospora, and fruit flies. The Salmonella/Ames test is the most widely used of the short-term tests, but may fail to detect certain classes of carcinogens. 9,12/ The procedure uses several specially developed strains of the bacterium Salmonella typhimurium. These strains contain different mutations, each of which is a defect in one of the genes necessary for the synthesis of the amino acid histidine. As a result, the bacteria cannot grow unless histidine is added to the growth medium. The mutagenic test is carried out by exposing the bacteria to the chemical to be tested, transferring them to a nutrient medium that does not provide the amino acid histidine, and then counting the number of bacterial colonies (from a standard inoculum of the treated bacteria) that grow in the absence of added histidine. Each such bacterial colony represents a mutational event that has restored the capability of a bacterial cell to synthesize histidine, i.e., the original mutation in the histidine gene has been reversed by another mutation. As the dose of chemical increases, the number of colonies increases until the effect plateaus or the chemical becomes toxic so that tests at higher doses are not possible. The method uses rodent or human liver extracts in the treatment mixture to provide the enzymes necessary to metabolize many carcinogens to their active form.

In the fruit fly (Drosophila), recessive mutations on the X chromosome can be detected by genetic tests. (Male flies have one X chromosome; females have two.) Usually in this method, male flies are treated with or fed the test substance and then mated with untreated female flies. If the chemical is a mutagen, the female progeny may receive, from their father, an X chromosome with an induced lethal mutation, but these females survive because they also have an undamaged X chromosome from their mother. When these females are mated to normal male flies, half of their male progeny will receive the "lethal" X and will not hatch. This can be detected as a reduction in the number of male progeny compared to the number of female progeny. The number of first generation females producing defective second generation male progeny measures the mutagenic potency of the chemical being tested.

Chromosomal aberrations induced by mutagens may be detected by observing the cell division process. Yeasts are frequently used to detect chemicals that cause chromosomal recombinations, a process that involves breaking and rejoining of parts of homologous chromosomes. It is also possible to examine directly human cells and chromosomes, for example by sampling blood cells. Among particular groups, such as chemical workers, who may be at high risk for chromosome damage, periodic examination of their cells ("cytogenetic surveillance") could help provide early warning of hazardous exposure.

- _Tests for DNA repair activity_ detect the ability of chemicals to damage DNA by identifying subsequent repair process. The unscheduled DNA synthesis test measures DNA repair in cultured human fibroblasts or other mammalian cells after treatment with the test chemical. In the Pol test, bacterial cells that lack a DNA repair enzyme do not survive in the presence of a test chemical that damages their DNA.
- _Cell transformation studies_ may approximate actual carcinogenesis most closely. _In vitro_ cell transformation tests measure the ability of a chemical to change mammalian cells into a form with altered growth properties, some of which are similar to the properties of cancer cells. The test is validated if a tumor develops when the transformed cells are reimplanted into a host with essentially the same genetic makeup as the animal from which the cells originated.
- _Promoter activity_ is detected by using a recent modification of an _in vitro_ transformation test. The test is based on the ability of a test chemical to reduce the concentration of a known transforming agent required to produce cell transformation. For example, saccharin itself is nontransforming but can act as a promoter to cause cell transformation by nontransforming doses of 3-methylcholanthrene. _36_/

Interpreting Results from Short-Term Tests

Short-term tests can be used in a number of ways not feasible with long, expensive animal tests. 10,11/ Because short-term tests are relatively easy, fast, and inexpensive to carry out, it is possible to do a large number of tests in a limited time period. This means that many different experimental conditions, such as concentration of the chemical, can be varied in a series of tests. It also means that the tests can be used to rapidly screen the large number of environmental chemicals, both naturally occurring and synthetic, to which humans are exposed. Therefore:

1. These tests may prevent unnecessary human exposure to mutagens. The mutagens may or may not be carcinogens. However, mutagens are of concern regardless of their carcinogenicity, because mutations in germ cells can be passed on to future generations.
2. The mutagenicity of a chemical may be traced to an impurity, and such knowledge could save a useful chemical.
3. Urine can be monitored to see if ingested compounds give rise to mutagens.
4. A sensitive short-term test may detect weak carcinogens that animal tests miss.
5. Short-term tests can help set priorities for further testing or regulatory actions.

Use of a group or battery of short-term tests will detect more carcinogens and mutagens than any single test since some tests may detect classes of compounds that other methods miss. Compounds that are positive in only some tests (for example, saccharin was positive in four out of a battery of 12 tests commissioned by the Office of Technology Assessment 18,33,34/) may be weaker mutagens or carcinogens than compounds positive in most or all tests. Use of more tests may also increase the number of non-carcinogens that give positive results in one or more tests (false positives). However, the status of these false positives is ambiguous. A compound may be considered a non-carcinogen if it gives negative results in animal studies, but it also is possible that an appropriately sensitive animal has not yet been tested.

Although an increase in the number of tests lessens the chance of missing potentially hazardous chemicals, this possibility cannot be completely eliminated. The number of tests chosen to investigate a particular substance's potential hazard should reflect the amount of uncertainty that is acceptable. A chemical to which there is likely to be high human exposure would require extended testing to minimize uncertainty. Conversely, for a low exposure substance, much more uncertainty may be acceptable, and only a few tests may be necessary. At present, it is not practical to set rigid guidelines regarding the short-term tests that should be used for a particular substance. In general, the initial tests chosen should be of several different types, and the choice should be partially based on data for chemicals similar to the one under consideration. Further testing then depends on early results.

Because of the possiblity of both false negative and false positive results, for regulatory purposes short-term tests in their present state of development should be considered in conjunction with animal or human data. A positive result in a well-conducted epidemiologic or animal study would override negative results in short-term tests. By contrast, a positive result in short-term tests might suggest that confirmatory animal tests be undertaken, but should not at this time form the sole basis for regulatory action, except in special cases.

More reliance probably will be placed on these tests in the future. Some industrial firms already stop commercial development of materials that give positive tests in short-term tests because of the increased risk that such substances will be carcinogenic in animal tests. Furthermore, regulatory agencies are undertaking studies to determine how these tests could most effectively be used for regulatory purposes.

Short-term tests are undergoing rapid development and validation as a means of detecting compounds that initiate and promote cancer. It would be extremely useful for these tests to become a reliable means of detecting cancer promoters. Detection of promoters may become a part of regulation in the future.

AN APPROACH TO IDENTIFYING MUTAGENS AND CARCINOGENS

In evaluating information about hazardous substances, the results most easily applied to assessing human health risk are 1) human data, followed by 2) animal data, and finally by 3) short-term tests. But the ease of testing is inversely related to the ease of direct application of results to humans. In testing new substances, the preferred order, based on practical and ethical considerations, would start with quick, inexpensive short-term tests, and move on if necessary to animal tests. Finally, even if testing does not suggest hazard, the substance should be monitored if human exposure occurs. Tests on a substance could stop at any stage, depending on the results obtained.

The following possible testing sequence for carcinogens depends on current information, and many modifications have been or could be devised. 37-39/ This sequence is based on the hypothesis that carcinogens are, or may be converted to, compounds that may damage the genetic material. It assumes that any compound that can damage genes is at least potentially carcinogenic or mutagenic.

Questions that can be answered experimentally are asked in the following order:

1. Is the substance genotoxic* to any living organism, either by itself or when appropriately metabolically activated?
2. Is the substance or its metabolites relevant to carcinogenesis as tested by in vitro transformation of mammalian cells and the ability of these transformed cells to develop into tumors in appropriate test animals?
3. Can the substance or its metabolites induce cancer or precancerous lesions in intact higher organisms, for example, as tested in long term animal experiments.

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* genotoxic: harmful to genetic material

4. Can the substance or its metabolites induce cancer in humans as indicated by epidemiologic data?

The first question may be best handled by a group of tests. Ideally, this first set of tests should produce no false negatives (i.e., no mutagens or carcinogens should remain undetected), although a moderate number of false positives are acceptable, since follow-up tests can be performed if desired. For carcinogens, if genotoxicity is not invariable, the testing process clearly should begin with Step 2. Also, the tests often will not proceed in sequence, since in some instances questions will be raised by data relevant to Step 4. However, the sequence indicates the direction in which thinking about test methodology currently is moving and provides a model for development of rational food safety testing.

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Chapter 6

CONCEPTS OF ASSESSING BENEFITS

In recent years there has been increasing interest in assessing benefits as well as risks when considering decisions about food safety. Although assessment of risks has become increasingly precise, assessment of benefits generally has suffered from a paucity of information and a lack of experience in applying the information that is available. 1-4/

This chapter summarizes some of the technical problems associated with assessing physical health benefits, and psychological, or perceived, benefits. It does not discuss economic factors, and therefore does not consider all classes of benefits mentioned in Chapters 3 and 4.

Types of Benefits

The categories of physical health benefits and psychological benefits overlap. Physical health benefits can be at least partially characterized physiologically or biochemically; psychological benefits are characterizable in terms of feelings, attitudes and perceptions. In either category, benefits may be direct or indirect. Direct benefits are first-order consequences, such as the cure of nutritional deficiency diseases by appropriate nutrient additions, as demonstrated by the effect of iodized salt on endemic goiter. Indirect benefits are illustrated by the prevention of botulism through use of nitrites; there is no direct improvement of health, but there is a reduction of a possible threat to health.

The categories differ in the techniques necessary to assess them. Direct physical health benefits are relatively easy to measure. Assessing indirect psychological benefits, however, is difficult because it requires comparisons of incommensurate values and many different individual and group preferences. 5-9/

A hierarchy of benefits might assign greatest importance to a direct improvement of health by the cure or prevention of disease, and least importance to benefits defined as esthetic or as matters of convenience. Within each of these broad levels of health benefits there might be gradations on the basis of criteria comparable to those applied to risk. Such criteria would include the importance of the benefit as measured or perceived, the number of persons benefited, the distribution of the benefit among special groups, and the relation between those benefited and those placed at risk. In most cases, the determination of perceived benefits may be expected to be imprecise and heavily dependent upon individual or collective judgment.

Assessment of Non-Economic Benefits

Although it is difficult to assess most types of benefits quantitatively, possible methods for assessing physical health benefits and perceived benefits are described below.

Physical Health Benefits

Many of the techniques for assessing physical health benefits 9-11/ are similar to epidemiologic methods for assessing health risks,* particularly because a health benefit can often be considered a negative health risk.

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*See Chapter 5.

Thus, the health benefits of a preservative lie in its ability to prevent the growth of bacteria that cause food poisoning. While much epidemiologic data is observational and subject to the limitations explained in Chapter 5, experimental studies (such as clinical trials or other intervention studies) may often be well controlled and therefore more useful in relating health effects to causes. Techniques useful for assessing physical health benefits include nutrition surveys, clinical trials, and studies of the quality of foods.

Nutrition surveys may be used to follow short-term or long-term nutritional changes. Changes occurring in the composition, quality, and quantity of food ingredients consumed, may be compared to changes in specific physiological parameters, such as the concentration of constituents of biological fluids. Choice of measurements would depend on the benefit(s) expected from particular changes in the food supply, e.g., the introduction of a food additive. Measurements may be:

- Dietary--changes in the variety of foods, in their amounts, in the frequency of consumption, or in the nutrient composition of the diet.
- Anthropometric--changes in the growth rates, as measured by height, weight, body circumferences, or skinfolds, although association of these changes with the presence of any single substance in foods may be difficult to demonstrate and unlikely to occur.

- Clinical—incidence of deficiency diseases; the overall level of nutritional status including over- or under-nutrition; specific diseases associated with specific food substances; or the incidence of chronic diseases associated with nutrition.
- Biochemical--changes in composition of biological fluids; changes in the storage, transport or excretion of substances; or tests of organ function.

At present, a number of features inherent in nutrition surveys limit their usefulness in assessing benefits of foods. Nutrition surveys are elaborate and costly, difficult to interpret, time-consuming, and require large populations. In some cases experiments with small numbers of subjects are possible if the experimental design allows the subject to also serve as the control (single subject design). (See Reference 12 for a detailed discussion of nutrition surveys.)

Clinical trials are especially applicable to assessing benefits of a long-term nature that might be expected in the case of chronic disorders, such as diabetes. In a clinical trial, two or more groups of people are subject to different treatments and the effects of the treatment are then noted. The confidence placed in the results of such a trial depends on 1) the magnitude of the change, 2) availability of adequate controls, 3) adequate double-blind test conditions, 4) suitable compensation for confounding factors, 5) replicability of the results, 6) the degree to which the test conditions reflect the "real world" of consumers, 7) appropriate quantitative measures, and 8) adequate follow-up.

The details of a clinical trial would depend on the aspects of the food supply under consideration. In assessing the potential benefits of saccharin, for example, one of the crucial unanswered questions has been the extent to which persons denied access to saccharin would substitute sugar or would forego sweeteners. A clinical test to study the effects of saccharin deprivation conceivably could be performed: a randomly selected half of an available saccharin-using population is instructed to avoid saccharin for an extended period of time, and comparisons are later made between the sugar consumption of the saccharin-avoiding group and the non-instructed group. While clinical trials are the most accurate method for evaluating benefits, problems exist. In this specific design, the subjects' awareness of their experimental condition could change their behavior.

A possibly more useful clinical trial of saccharin would compare health effects, such as relative weight loss, between a test population of saccharin users and a control population that does not use saccharin. However, because it would be impossible to control the dietary intake of the study population, results would not be completely reliable.

Ethical considerations play a major role in the conduct of clinical trials. Experimentation with human subjects is now carefully controlled, and exposure of test subjects to substances in foods with known levels of risk can be justified only by the expectation that substantial benefits can be gained. In such circumstances, protection of test subjects, including procedures for ensuring that the informed consent of study participants is obtained and that acceptable testing procedures are adhered to, generally preclude clinical trials from producing expedient results.

Nutritive quality of food ingredients may alter as a result of particular changes in the food supply. Measurements of nutritive quality may be a valid first indicator of health benefits from such changes in the food supply. Measurements of food quality could include:

- Changes in the solubility or the absorption of food ingredients.
- Improvement in the nutritional quality of foods, such as by amino acid supplementation.
- Changes in growth-promoting ability of foods or of single ingredients in foods, as tested in animal experiments.
- Changes in the nutrient content of an average diet because of the addition of foods containing nutrient supplements.

Psychological or Perceived Benefits

Various characteristics of the food supply that may be desirable do not necessarily affect physical health. These characteristics involve taste, appearance, convenience, and familiarity. They may contribute to psychological wellbeing by giving pleasure and satisfaction.

Psychological benefits have not been considered extensively in past food safety regulation, and methods for assessing these benefits are poorly developed. However, the absence of methods may have resulted more from lack of experience in measuring such benefits than from limitations on what may be possible. The discussion that follows is therefore speculative, with emphasis on what might be done in the not-too-distant future.

It is sometimes argued that factors that cannot be precisely measured are intangible and probably not important as a basis for policy decisions. There is no logical reason, however, that the importance of a factor should be related to its ease of measurement. Much that is trivial can be easily quantified, and much that is consequential eludes exact measurement. The importance of subjective factors in food safety is made clear by the controversy surrounding saccharin. Although psychological benefits related to the use of saccharin and other non-nutritive sweeteners cannot be readily evaluated at present, large segments of the population appear to regard the substance as desirable. 13/

Two general strategies have been used in attempts to assess the perceived or subjective benefits associated with risky activities in general: revealed preferences 14/ and expressed preferences. 15/ In the method of revealed preferences, the amount of money spent by the average individual on a voluntary activity is taken as an index of the overall de facto benefit of the activity. While money spent may be the observable behavior most relevant to food preferences, other behaviors such as amount of time spent, could be observed for particular voluntary activities. 16/ In the method of expressed preferences, persons indicate to a survey interviewer their judgments of the benefits they perceive from an activity.

Both methods are controversial. 17/ Objections to the revealed preferences approach are that past behavior may not be a valid indicator of present preferences and that incomplete information, biased perceptions, and market structure may prevent people from making decisions reflecting "true preferences." Objections to expressed preferences are that people may give socially desirable responses to interviewers, that their verbal responses may not predict behavior, or that survey measurement of benefits could be subject to attempted manipulation in publicity campaigns. In applying these methods to food safety, expressed preference methods seem somewhat more straightforward than market analysis methods, but both need much further evaluation in terms of utility and reliability.

The two major possibilities for expressed preference measurements are surveys and taste tests.

Methodologies for conducting surveys of public reactions in a variety of domains have become increasingly sophisticated in the past 30 years, 18/ both in the sampling of respondents 19/ and in the careful phrasing of questions to avoid artifacts. 20,21/

The major problem in applying these methodologies lies in attempting to measure absolute benefit directly. Attempts to measure the benefit of one substance relative to the benefit of another--relative benefit--may be more meaningful and feasible. To illustrate, public opinion surveys before elections compare alternative candidates; such results usually correlate well with election results. Many years of experience with comparative surveys demonstrate their special usefulness in measuring benefits. Respondents can more consistently agree on the relative benefits of various objects, such as bicycles, power mowers, or cars, than they can judge relative risks of those same objects. 22/ The explanation appears to be that people have repeated and regular experiences with the beneficial properties of objects, but only rare and scattered exposures to their hazards.

In food safety, scales of relative psychological benefit within different substance sets could be developed by posing comparative questions: which substance do you prefer, which would you miss most if it were banned, etc. Alternatively, different substances can be placed on common rating scales, using several standard methods. 23-25/

Measurement of relative benefits offers several advantages. Scales of relative psychological benefits could be subdivided by different population groupings, thus establishing whether different subjective benefits are obtained for groups exposed to different levels of risk. Use of relative benefit measurements could serve to achieve consistent and comprehensive evaluation of all types of benefits and for different types of substances. Natural food substances, GRAS-listed substances, and recent food additives could be placed within the same policy logic because they would be ranked on a common benefit scale. This ranking would also allow for comparisons of health benefits, perceived benefits and economic benefits.

In instances where products are not known by name, comparative benefits can be assessed by taste panels, or by other comparative exposures. There are two common approaches to establishing taste panels, which are particularly applicable to testing sweeteners and food additives. 26/ The first method uses small expert screening panels for quick evaluation of taste impressions. Panelists are required to use a series of reference standards with which to compare the new substances on various dimensions of taste, such as sweetness or bitterness or even less defined characteristics as "off-flavor." A variant of this method is known as the flavor profile. 27/

In the second approach, the members of the taste panel use rating scales or magnitude estimates to evaluate overall preference for the substance. In doing this, they may also provide a description of the taste.

Taste panel research is uniquely suited to deriving stimulus-response curves (or "psychophysical functions") for subjective sensations, which vary as a substance's concentration in solution is changed. These functions can have important implications in balancing benefits against risks. For example, it is well known that the perceived sweetness of saccharin solutions levels off above a certain low concentration of saccharin, and at somewhat high concentrations, the pleasantness of the taste drops because the bitterness component predominates. 28,29/ Thus, taste panels could help determine the minimum amount of saccharin required in diet foods to produce a sufficient level of sweetness.

The Context of Assessment

The assessment of health benefits should be viewed in the context of the circumstances in which it might be used. As can be seen in the decision framework of Chapter 4, there are two major kinds of circumstances in which a benefit assessment might be advantageous (see Step D in Figure 4-2):

- A substance is known to have some risk associated with it, and a potential substitute with negligible risk is proposed. If this "substitute" is publicly acceptable, then the issue may be resolved by banning the more risky substance. The question of when a substitute is a good substitute is the question of relative or comparative benefit. The procedures outlined above are direcly applicable. If the substitute substance is comparable in level of benefit to the original substance, the question is answered. Only if the substitute is dramatically lower in benefits does the dilemma remain.
- A substance is known to have some risk associated with it, but no substitute is available. The question is whether the benefits of the substance are great enough to warrant keeping the substance on the market, with appropriate risk warnings. A more elaborate version of the same question arises when a substance is judged to carry such an appreciable risk for one segment of the population (e.g., children) that restriction of access to that segment is recommended. Then the question is: "Should such restrictions apply generally to the population or are the benefits to the remainder of the population

> sufficient to warrant a policy of varied restriction?" In this case, the problem is whether the absolute level of benefit is high enough to compensate for a given degree of risk. This may be termed the question of absolute benefit.

The assessment of relative benefit does not directly address the question of accompanying risk because the degree of risk that society would be willing to accept to achieve a particular level of benefit is unclear. However, an indirect assessment might sometimes be achieved by comparisons among substances. Suppose that saccharin and another substance have roughly comparable risks, but saccharin has greater physical and psychological health benefits. Then if the decision is made to ban or limit saccharin, consistent policies would suggest, at a minimum, restrictive treatment of the other substance.

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Chapter 7

INFORMATION, EDUCATION, AND FOOD SAFETY

Recent events and public concerns about food safety suggest a need for an improved information base for regulatory decision-making and for better communication between regulatory agencies and the public. An effective regulatory system should include: information about exposures to enable recognition of risks and benefits to the average person and to special subpopulations; scientific input and advice; effective communication of information to consumers to allow informed choices in the face of uncertainty and possible risk; and public participation in the regulatory process.

Although some actions mentioned in this chapter could be implemented relatively quickly, many of the proposals are feasible only in the long run. The development and implementation of extensive new systems of food safety monitoring and surveillance, for instance, are not imminently feasible. Changes in patterns of training scientific personnel also require time and evaluation. Other proposals in this chapter are currently feasible, but in need of detailed research prior to making major commitments to specific approaches. For example, there is little information available on the most effective methods for providing information to the public. While increased public participation in the regulatory process is a worthwhile objective that might be accomplished in a relatively short time, many alternative methods need to be evaluated thoroughly.

RISK RECOGNITION

Monitoring and surveillance of substances in foods are a necessary part of a food safety policy. Food-related disease incidence, the food itself, and the amounts people eat may be monitored.

Systems for monitoring health effects are generally more feasible than those for monitoring foods. Because of the very large number of variables associated with the food supply, it is extremely difficult to devise systems that will detect unanticipated effects of food ingredients unless these effects are dramatic and frequent. Systematic surveillance may, however, be useful in verifying hypotheses regarding the health effects of a specific substance, or in looking for effects attributable to a specific substance. A system for seeking biologically or socially important rates of toxicity or health benefits that could be attributed to foods or food additives has not been devised. Although the difficulties are recognized, some of the methods that might be useful in detecting health effects of substances in food include 1) centralized information banks, including disease registries and specimen banks, and 2) exposure studies, including studies of diet and food components.

Centralizing Health Effects Information

Central reporting systems provide a way of linking data from diverse sources. Many initial observations of new or rare diseases come from alert clinicians, public health workers, and others. These scattered observations become useful when they are integrated in meaningful patterns. 1/

At present, appropriate methods of linking scattered individual observations are limited, partially because of the problems involved. Of particular concern is confidentiality, since central reporting that permits retrieval of information by various authorities or researchers may violate a person's privacy. Appropriate safeguards are necessary to protect privacy without forfeiting the opportunity for further observation and possible intervention.

One limited example of an approach to centralized disease reporting is offered by the Center for Disease Control (CDC) of the Department of Health, Education, and Welfare. Concerning foodborne diseases, CDC tabulates information provided by private physicians, the armed forces, state and local health departments, FDA, and USDA. 2/ While CDC has been concerned primarily with acute infectious diseases, it has increased its interest in chronic disease distribution and etiology and in diseases associated with environmental contaminants. 3/ Occupational exposures are of special interest (aside from the health of workers), because occupational exposures may provide useful clues for seeking a particular effect of a substance in larger populations.

However, as discussed in more detail in Chapter 5, information about the incidence of disease does not by itself provide information about the cause of the disease. Ferreting out the causes of a disease requires detailed information about people who are not diseased (case-control studies). Currently in the United States, efforts to protect a patient's privacy make it exceedingly difficult for an organization, such as CDC, to obtain additional data on individual cases of disease.

Information on Substances

Central data systems may classify information by chemical compound rather than by disease. Information from accidents, occupational exposure, and animal and other studies can be computerized and available in a central location. As an example, the International Agency for Research on Cancer (IARC) collects information on carcinogens from animal and epidemiologic studies. 4/ In recording information from studies involving human subjects, problems relating to confidentiality remain.

Specimen Storage

Stored samples of foods and human tissues have proved useful in diagnosing diseases retrospectively. These samples can serve as historical records of past exposure levels. Thus, human breast milk collected by EPA several years ago for one purpose served as a valuable but unplanned source of data on polychlorinated biphenyls (PCBs). 5/ Preserved museum specimens of birds and fish have been used as pollution indicators for mercury. 6/ Blood, serum, hair, and teeth are among specimens that have revealed past human exposures to environmental hazards. 1/

Food Consumption Data

Analysis of actual food samples gives information on concentrations of contaminants and food ingredients. These data are useful for suggesting hypotheses for further study, such as a connection between aflatoxin in foods and liver cancer. The hypotheses may be strengthened by information about the actual intake of substances by population groups, especially groups that may be at special risk. Efforts to obtain reliable consumption data are being made, but these efforts are expensive and fairly recent, and techniques are still being developed and tested. Because these data may help guide food safety efforts towards the foods and population groups that most need attention, their continued development should be encouraged.

High Consumption Groups

A few surveys have examined food consumption patterns of individuals, but these surveys are usually not concerned with disease outcome. The USDA 7/ and the Market Research Corporation of America (MRCA) 8/ have conducted surveys in which families record what they eat during an entire day (USDA) or during a two-week period (MRCA). Because food consumption varies greatly among individuals, these types of studies estimate different levels of intake and allow identification of groups that may be at special risk because of high consumption of certain substances.

The importance of monitoring the intake of these groups is two-fold. First, appropriate regulatory policy may differ if one percent of the population eats 99 percent of a product compared with a more evenly distributed consumption pattern for another product. A flexible regulatory system possibly could protect high level consumers without infringing on the choices available to other consumers. Second, analysis of identified high level consumers might suggest associations between specific substances and specific diseases that would not be detected among average consumers.

Special Risk Groups

Consumption patterns of population groups who are especially susceptible to toxic substances need to be analyzed. At present, concern rests primarily with four population groups:

1. The pregnant women and the fetus. During critical periods of fetal development, organ systems are exquisitely susceptible to disruption of normal patterns of differentiation and growth. Intrauterine exposure to toxic substances is potentially more

harmful than exposure at other times of life. Although the maternal metabolism and the placenta limit fetal exposure to some toxic substances, many toxic substances enter the fetal circulatory system. The fetus is particularly susceptible to toxic effects because of its limited detoxification ability. 9/ Knowledge about the food intake patterns of pregnant women is therefore important to the protection of the fetus. Better methods are needed for monitoring fetal exposure to toxic substances.

2. The infant. Chronic exposure to toxic substances during the first year of life is of special concern particularly because body organs and tissues are undergoing extensive growth and development during this period, and may be more susceptible to toxic substances than those of an older person. 10/ Because harmful effects from exposure to some substances appear only after many years' latency or after prolonged exposure, it is especially important to protect infants. Toxic substances in an infant's diet can include those found in breast milk of women exposed to environmental contamination.
3. The child. Toxic substances consumed during childhood may pose a higher risk to health than would the same substances consumed by adults, because children consume larger quantities of food per unit of body weight than adults. Recent data suggest that consumption of saccharin by children under 10 years old is increasing and that they may have a higher intake of saccharin per unit of body weight than any other age group. 11/ Such

information may be useful in developing regulatory strategies to protect children, who have a longer available time for exposure and for development of diseases with a long lag period than adults.

4. The elderly. Evidence is accumulating that the body's detoxification ability changes with aging, which suggests that the elderly may have a greater susceptibility to harmful effects from exposure to toxic substances. 12/ Long latent periods are not of as great concern as for younger groups.

Multiple-Source Exposure

Toxic substances enter the body through many routes, including inhalation, ingestion, and absorption through the skin, and from many sources in the environment such as foods, water and air. Because the risk of inducing disease tends to be associated with the amount of a substance that enters the body, as well as interaction among different substances, monitoring of exposures should not be limited to one regulatory area or to single substances. Greater emphasis needs to be placed on the total burden of intake, including substances in foods, particularly for special population groups. Occupational exposure to toxic substances at high levels or for extended periods, 13,14/ may result in adverse effects appearing in workers before they appear in the general population whose exposure is more limited. Exposure to toxic substances or agents in the workplace may enhance the effects of other environmental hazards. Such interactions may be especially important in the development of cancers.

Improving Surveillance

Many possibilities exist for improving surveillance and monitoring systems for detecting possible effects of food substances on disease. Since acute dramatic effects will usually be recognized without special effort, the emphasis should be on the detection of subtle but serious effects. For example, the causes of an increase of a few percent in the incidence of heart disease would be difficult to detect but would affect many people. When past exposures cause diseases with long latent periods, determining causative relationships is especially difficult; people do not know much about the food ingredients they consume at present, and they know even less about their exposures to substances many years in the past.

Despite the difficulties, some approaches may be more fruitful than others, and further research would help determine which of the following areas deserve emphasis.

Centralizing Information

- Systematic registries arranged by substance to combine information from many sources could be desirable. Information would include data on short-term tests, animal studies, occupational exposure, and epidemiologic studies. Such registries might follow persons known to have been exposed to particular substances. 15/ Data from outside the United States should be included.
- Appropriate centers could serve as data banks on diseases that might be related to environmental exposures, including food additives and contaminants.

- Health workers could be alerted to watch for unusual disease patterns, and to report such clinical observations to an appropriate center for follow-up to establish statistically significant relationships. Special training could be provided so that, for example, health workers in obstetrics and pediatrics could be particularly aware of possible effects of toxic substances in food on diseases in pregnant women, infants, and children. These observations could help detect unknown or unexpected health effects, since several isolated cases may turn out to have factors in common that may suggest a cause of the disease.
- Systematic specimen banking could be developed. The availability of tissue specimens and food samples can prove invaluable in testing hypotheses concerning the health outcome of past exposures to toxic substances. Stored samples may provide the only way to obtain data on past exposure to substances that currently are not known to pose hazards.

Food Consumption

- Individual consumption data are needed to help identify high consumption or highly susceptible groups. Present systems of data collection tend to under-represent children, the elderly, and the poor, even though these groups may be especially susceptible to toxic substances. Pregnant women and infants also require special attention.

Multiple-Source Exposure

- Coordination of surveillance and action across regulatory boundaries may be important to protect individuals based on the total body burden of exposure to different sources of toxic substances. Interaction of occupational exposures with other sources of environmental exposure may be especially important.

SCIENTIFIC EXPERTISE IN REGULATION

In making food safety decisions, regulatory agencies usually need more or different scientific information than is available. Until now the regulatory agencies have had to rely to a great extent on data submitted by outside sources—often the regulated industry—without necessarily having adequate internal resources to evaluate the validity and adequacy of submitted information.

Regulatory agencies have a unique need for research that is impartial as well as relevant to the decision-making process. But regulation-oriented research often is not of high priority or interest in the general scientific community, despite the rapidly rising need for evaluating potential health hazards associated with chemicals and other technologies. Mechanisms are needed to promote basic research in the development of methodologies and education programs that would encourage research relevant to the regulatory process. Research areas that could be enhanced include: toxicology; epidemiology and disease surveillance; food consumption surveillance; methods for assessing risks and for assessing benefits; and clinical trials to test substances.

Few of the thousands of existing food substances have undergone extensive toxicologic testing. Safeguarding the food supply requires at least preliminary data on risk for a large number of substances, followed by more extensive assessment of both risks and benefits for those substances that may enhance or reduce their combined toxicity. For example, in laboratory experiments selenium has been reported to neutralize the toxic effects of methylmercury in certain animal species. 16/

Testing and research activities by the several regulatory agencies involved in environmental health may be duplicative, even when done through the contract mechanism. Improved efficiencies might be achieved through coordination by an interagency group (such as the existing Interagency Regulatory Liaison Group), or the responsibility might be assigned to a new center. The objective would be to increase safety testing by targeting research to areas of greatest need.* Such an entity could be located as a separate unit within a regulatory agency, or it could function independently. The latter possibility seems more likely to attract the necessary multidisciplinary expertise of high quality. Once assembled, such a staff could be valuable in general toxicologic and epidemiologic research as well as in meeting other specific needs of the regulatory process, such as setting up clinical trials or food consumption studies.

The existence of an appropriate institutional locus (center, institute, agency) would, in itself, increase the visibility of the needed activity and emphasize the importance of training and recruiting suitably motivated personnel. Because currently there is a concern about a possible oversupply of biomedical technical personnel (at least in the short-term) as well as an expressed need for toxicologists and epidemiologists, 17/ a shifting of resources to areas of research and training oriented to regulatory needs may be possible and desirable. A strong institutional locus may help promote such transfers.

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*For example, in November 1978, Secretary of HEW Califano announced the establishment of a National Toxicology Program, which involves pooling of resources of four HEW agencies—NCI, NIOSH, NIEHS, and FDA—to improve research, detection and control of toxic substances.

Another problem relates to the proper recording and utilization of data on risks and benefits. Standard scientific procedure places heavy emphasis on refereed publications and the necessity for independent confirmation of data. Analysis related to environmental regulation, however, frequently is carried out under heavy public pressure for quick results. In the saccharin case, for example, data became critical in a regulatory decision prior to their publication, and this, together with agency timing and reporting of the data, may have been factors in the public reaction. Furthermore, in studies designed to assist regulatory decisions, there often may be no incentive to repeat the study once a decision is made. FDA has recently issued regulations on the procedures to be used in generating and utilizing data for regulatory purposes in order to ensure that the data generated are valid. 18/ This effort should be strongly encouraged, and supported, particularly where data are generated through contract mechanisms and are not published in reputable, refereed journals.

A conflict often seems to exist between the need for regulatory expediency and the need for time-consuming rigor in scientific investigation. This conflict, however, may be reduced by encouraging patience in the regulatory process under some circumstances. Where risks are relatively small, and exposure to the substance has taken place over a long time, the regulatory process should ensure standard scientific rigor as fully as possible. Of course, where a serious risk is identified, prudent regulatory practice would require interim action on the basis of tentative scientific findings.

PROVIDING INFORMATION TO THE PUBLIC

When the risk from a food substance is not substantial enough to warrant banning, it might be appropriate to provide information so that the risk-taking decision is left to the consumer. Such a policy can be especially useful in cases 1) where risk is possible but infrequent, and not severe or disabling, and is balanced by perceived benefits, or 2) where the regulatory strategy is directed at a limited population group, such as a high-consumption group.

This strategy of informing the consumer of risks should generally be used in combination with other approaches. It need not allow permanent use of substances in foods with a known risk, unless no alternatives are available. Industry should be encouraged to develop safer substitutes when possible, especially because there may be some decrease in health risk from using several different substances rather than relying only on one to achieve a particular purpose. Industry also should be discouraged from continuing to produce the risky substance. (It may be possible, for example, that the concentration of saccharin in diet soft drinks could be reduced without a loss of taste or a gain in calories. 19/) However, while the risky substance is on the market, an information strategy could encourage voluntary reduced use of the food substance, especially by segments of the population that benefit least from the substance or food.

Many difficulties arise from attempts to provide risk information to the public. First, it is not easy to convey warnings about small and ambiguous risks. People have difficulty conceptualizing small-probability hazards, 20/ and abstract statistical information is much less compelling than concrete information. Second, the scientific basis for assuming the presence of food risks is often subtle and vulnerable to public skepticism. High-dosage studies in rats fall in this category. Third, there is a danger that the public is satiated with health danger warnings, and would pay little attention to any given warning because of an increasing perception that, for example, "everything causes cancer." Fourth, public trust in the actions of government appears to have declined over the last ten years, 21/ and a lack of credibility of government-sponsored information may limit its effectiveness.

Public education is only effective in promoting healthful behavior if members of the public choose to alter their lifestyles in response to the information they receive. At present, knowledge about the effectiveness of health education is limited. Many health educators believe the public is inattentive to isolated messages. Even with a great deal of forceful repetition—beyond the budget of most health education programs—there may be little public response. Part of this assessment may be due to anticipated response levels that are unrealistically high, at least as compared with those of private industry, which is an experienced modifier of American behavior through advertising. 22/ (Private industry is usually satisfied with a two percent sales gain from a promotional advertising campaign on television.) Convincing people to modify their diet in ways intended to improve health is difficult. Concerted efforts have been made with some success, in recent educational campaigns aimed at getting people to reduce dietary fat and cholesterol content. 23,24/ We do not know if it is possible to generalize from the results of these campaigns, which involved relatively common foods and food constituents, to the effectiveness of informing consumers about small risks associated with obscure toxic substances. Furthermore, observed dietary changes towards lower fat and cholesterol consumption have been supported and probably reinforced by commercial media campaigns that promote the sale of products low in these substances.

The effectiveness of labeling as a strategy to promote healthful behaviors is not clearly determined because it is difficult to isolate the impact of labeling from other factors. Much of the current research on the effect and utility of warning labels has been on labels on cigarette packages and their impact on smoking trends. These studies indicate both encouraging and discouraging trends in smoking in the U.S. population. A recent major study of smoking patterns since the cigarette package warning label was introduced, concurrent with the general antismoking campaign, shows that smoking rates in adults, particularly men, appear to be on a downward trend. 25/ However, smoking rates for adolescent girls are increasing, 26/ as is the use level per smoker. 25/* It is difficult to correlate these trends with existing studies on the effectiveness of antismoking public education campaigns. A thorough review of available literature on smoking education programs between 1960 and 1976 concludes that most attempts to influence the smoking behavior of youths have had little success in the United States. Antismoking campaigns directed at adults also have been ineffective, although smoking withdrawal clinics and individual counseling have produced positive results in 20 to 35 percent of participants. 28/

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*These trends agree with findings of the report on smoking and health recently released by the Surgeon General of the United States. 27/

The limitations of existing knowledge notwithstanding, an information strategy should probably consider the following factors:

a) Usefulness. Information should be oriented toward what people might do, beyond simply what they ought to know. This would include providing information about concrete alternative actions that people might take, with specific reference to populations that are at higher-than-normal risk.

b) Appeal to common sense. Information should be concrete and clear.

c) Credibility. Information should be presented in as honest and straightforward a manner as possible, avoiding the impression of fudging or artifice.

Information Devices

Warning Labels

Additional research and attention to past research might lead to more effective warning labels. The major example for food additives is the saccharin label currently in use (both on products and in stores), which states, "Warning. (This product contains) saccharin, (which) has been determined to cause cancer in laboratory animals." We know of no study that specifically addresses the effectiveness of this warning, but in all likelihood it is ineffective because it employs a fear appeal without a concrete recommendation for how the reader should respond. This combination is ordinarily unpersuasive 29/, and stands to be even less persuasive because of public skepticism surrounding anti-saccharin actions.

Without proposing specific language, an alternative label could be devised that considers the three factors discussed above. The warning should be stated clearly, and it should propose a course of concrete action. High-risk population groups should be identified. In order to be credible, the message should not be fear-arousing, and should probably avoid reference to scientific procedures that may not be meaningful to the general population, without adequate explanation.

We do not know the extent to which consumers would respond to a specific labeling format. No objective quantitative data on risk are usually available to consumers, and qualitative estimates of risk may never be able to provide all consumers with meaningful information. However, an extremely cautious and generally well-informed consumer would probably avoid substances labeled as low risks, except when there is a substantial benefit and there are not acceptable substitutes. A moderately cautious consumer may merely try to restrain the total use of risky substances singly and in combination with other substances, especially during periods of vulnerability such as pregnancy. Other consumers may pay no attention to risk labeling.

Risk Logos

The use of distinctive graphic symbols (logos) to indicate possible risks in non-food areas, such as the warning symbol for radioactivity, suggests that distinctive logos prominently displayed on food packages might aid consumers in identifying risk.* Experimental use of logos would be necessary to determine their effectiveness.

The purposes of the logo would be two-fold. First, the logo would inform the consumer that the product belongs in a certain risk category, thus implying the degree of caution that the consumer should exercise.

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*See Chapter 9 for discussion of risk categories.

Second, the logo could direct the consumer to sources of additional information. Thus, for products with a "high risk" logo, separate circulars could be attached to or provided with the product. For products with a "moderate risk" logo, the place of sale could be required to have additional information available on request. The information provided might parallel that provided with some drugs, and would be more comprehensive than the limited space on a food wrapper allows. Information would include the nature of the product, risks to special population groups, suggested limits on intake, and possible adverse interactions with other foods or substances. Logos are easily recognized, and could help consumers distinguish among risks.

Logos present obvious problems that require careful consideration and study. Some of these are:

- Consumer understanding How can consumers best be educated about the relationship of specific logos to specific risk levels? Will consumers understand the intent of the logos and accordingly make informed decisions? Will they seek out and examine the information available to them? How can those population groups who are not reached by information strategies (e.g., children and functionally
- Information mix How should the use of the logos and other sources of information be coordinated? Should logos replace traditional warning labels on containers, or should both strategies be used simultaneously? How should additional information be provided (e.g., attached to the food container or in separate leaflets)?
- Institutional food services and vending machines How should information be provided for foods sold in places other than

food markets? Of special concern are restaurants, cafeterias, vending machines, and institutional services such as hospitals and prisons. If the information cannot be provided in these situations, how should consumers be protected?

- Costs Is this strategy feasible in light of practical problems and costs? How should the responsibility of providing information be distributed between the government and/or the producers and how should costs be passed on to consumers (e.g., indirect taxes, direct taxes, or higher product prices)?

Other Information Devices

Labels cannot carry the entire burden of an information policy. Some information to the public on the overall quality of the food supply is necessary. One way in which the public might be kept up to date would be a "Yearly Report on Food Safety," covering the development of new substitutes (such as sweeteners); intentions to reexamine data on substances previously considered risky (e.g., cyclamates); substances newly classified as to risk, with an explanation; coverage of reliable major scientific studies on food safety (e.g., epidemiologic studies of particular diseases); and so on. The intent would be to convey both positive and negative developments and to help counter confusion, alarm, and cynicism about food safety.*

Another source of information might be a reference book complied by FDA with sections on the status of particular substances and particular disease categories, and explanations of the types of scientific evidence leading to risk classification. This book could be available in all large supermarkets.

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*This proposal should be coordinated with other proposals being made in this area. As examples, 1) P.L. 95-623 (1978) requires reports every two years on the risks and costs of environmental pollution from human activities 30/, and 2) a 1978 amendment to the National Cancer Act of 1971 requires annual reports on carcinogens, human exposure to carcinogens, and the effectiveness of regulatory efforts to reduce exposure.

Eventually, food safety information might be made available to the public through innovative methods. Interested consumers might be reached by computer terminals or audio cassettes, and other means in addition to print communications. A greater reliance on the information media, especially television, seems to be appropriate, and the possibility of requiring safety information as part of commercial advertising should be considered. Ultimately, government has the responsibility for initiating programs so that food safety information reaches as broad a public as possible.

The Prospect of Information Strategies

An active and growing number of consumers is interested in food safety information. Adequate information made available to concerned and interested consumers could help raise the general level of public sophistication in making informed choices and promoting actions that individuals can take to safeguard their health. The effectiveness of information in achieving these goals, however, remains to be determined. Although the effectiveness of various types and combinations of information devices is poorly understood, several conclusions about disseminating food safety information can be made.

First, food labeling has the potential to provide consumers with a wide range of information that may be important to health, but this potential has not yet been achieved. Groups with special health concerns find that labels often lack specific and important information. The

United States Department of Agriculture, the Food and Drug Administration, and the Federal Trade Commission have been holding public hearings to learn consumer views on labeling. Logos could be studied as a means of identifying categories of risky substances.

Second, since food labels can provide valuable health-related information, they enable many concerned individuals to make informed choices based on their own assessment of risks and benefits. In practice, people with intolerance to certain food substances require adequate information in order to avoid those foods that produce ill effects.

Third, warning labels on certain food substances may provide a compromise between banning a food or allowing completely free distribution, but their proposed use on food products should be considered in the light of limited evidence of success.

Fourth, research is needed to evaluate and enhance the effectiveness of labeling in a food safety information program. Labeling should be only one part of a broad information strategy designed to provide information at different levels of sophistication to reach as many consumers as possible.

Fifth, the responsibility for initiating effective food safety information strategies must rest with a federal government agency, notably FDA. This agency must 1) ensure coordination in the information provided by different public agencies in order to prevent confusion; 2) develop improved coordination across regulatory sectors to promote cohesion in the government's approach to environmental safety; and 3) seek to constantly update information programs to take advantage of new knowledge about information dissemination strategies and new technologies for transmitting information.

In a discussion of informational and educational strategies for the public, the role of formal educational institutions is of utmost importance. The committee did not have the opportunity to pursue this subject in the time allowed but recognizes that in meeting the public's information needs for an effective food safety policy, the institutions and agencies whose mission is education have a crucial role to play. Education on foods, food safety and nutrition in schools at all levels hleps provide the background necessary for people to exercise discriminating choices. In the absence of a more formal educational background, campaigns of public education run a high risk of being ineffective.

PUBLIC PARTICIPATION IN THE REGULATORY PROCESS

In the past few years, increased attention has been focused on processes of direct public participation in regulatory activites of federal, state, and local governments. Public involvement appears to be especially desirable in food safety regulation, an enterprise that affects choice in the personal matter of diet.

Functions of Public Participation

Public participation in regulatory activity allows the agency and the public to exchange views. The expression of many attitutdes and concerns informs the agency of the spectrum of public feelings about the consequences of regulatory options under consideration. Such participation includes opportunities for consumers, producers, and other interested groups to influence agency decision-making and to help the agency strike an appropriate balance between government regulation and private decision-making.

Public participation also presents opportunities for the agency to communicate with the public. Thus, people can become better informed about agency policies, actions, and limitations. Such increased public awareness helps to promote public trust in agencies that fulfill their mandate properly, and to encourage change in agencies whose procedures require improvement.

Forms of Public Participation

Major forms of public participation in regulatory processes are: public comments; agency information collecting; and public membership on official committees. The public also can petition FDA to initiate action. FDA and other public agencies could increase public participation throughout the regulatory process.

At various stages in the regulatory process, FDA now invites public comment. After FDA publishes a proposed regulation in the Federal Register, individuals or groups may send their comments to the agency, which considers these comments before issuing final regulations. Because few citizens have the time and inclination to examine the Federal Register daily, in practice this procedure is more available to organized groups, including industry, than to individuals.

Public comments can also be made at informal hearings, which FDA often holds before issuing a final regulation. A hearing offers organized groups and those who are not collectively organized an opportunity to state their views. To enable individuals to participate in hearings more easily, FDA and other federal agencies are experimenting with holding hearings on the same subject in different parts of the country. FDA, USDA, and the Federal Trade Commission used this procedure in 1978 for hearings on nutrition labeling of foods.

Existing public comment procedures have advantages and limitations. Effective comment procedures allow expression of all points of view: consumers, organized or unorganized, with specific non-health concerns; researchers; small farmers; and advocates of nonconformist philosophies. From a regulatory viewpoint, when reviewing agency decisions, courts can consider the widespread views that are on the record. Much public comment is anecdotal rather than scientific, and the expressed views may reflect the intensity of various people's opinions as well as the diversity of public opinion. Also, purely individual participation in public hearings has usually been limited to those who could take time away from work and pay their travel expenses.

It might be advisable for agencies to invite public comment before a regulation reaches draft form, instead of waiting until after drafting the regulation. For instance, the 1978 nutrition labeling hearings have allowed consumers to influence the regulatory process in an early stage, rather than merely to respond to agency initiatives. Early public comments might help agencies establish regulatory priorities.

To encourage more public comment, FDA could expand its Office of Consumer Affairs mailing list, which alerts recipients to agency activities. The agency also could intensify outreach efforts to receive information from individuals with special concerns. A method of reimbursing some consumers for their travel and time might be considered.

To promote interest and knowledge in food safety regulation, new initiatives in health education may be desirable. An important first step could be to expand research on the effectiveness of various educational approaches.

Collecting Information

FDA could expand its use of existing systems for gathering information about food. Such systems include public opinion, product experience, and market research surveys. Although collection and analysis of data on public attitudes and experience would be expensive, results of such studies could help balance individual and group views expressed as public comments, and could help FDA become aware of consumer satisfactions and distresses.

Complaint data could be more fully coordinated so that the agency systematically becomes aware of relevant information contained in consumer letters to producers, industry-monitoring associations, and government officials. Lawsuits and disease-reporting systems also could serve as information sources.

Collection of information on public attitudes toward food safety regulation could also be given greater emphasis. Surveys are one way of learning about public views. FDA also could experiment with an ombudsman channeling concerns about food safety and food safety regulation.

Public Membership on Official Committees

Officially constituted advisory committees may be of substantial help to the responsible regulatory officials. Such committees may appropriately include both industry and consumer representation, and serve as forums for improved communications between producers and their customers. FDA recently has made extensive use of scientific advisory committees that include non-voting consumer and industry representatives. These representatives serve as liaison between their constituencies on the one hand and voting committee members and the agency on the other.

In a variation of the jury system, persons from some array of interests might be selected to serve on committees established by the regulatory agency. Colleges and universities could provide additional training in consumer representation (including advocacy skills, technical information, and business management) so that consumer and other representatives could participate as peers of committee members with considerable expertise in the regulated area.

Another approach to public participation is to enlist the responsible advice of especially interested or well-informed individuals who are affiliated neither with the regulated industry nor with research in the regulated area.

Greater consumer and industry participation, however, is no substitute for participation by scientists and other experts in diverse fields. Interdisciplinary scientific advisory groups can inform the regulatory process about the latest scientific developments and can help achieve a scientific consensus among toxicologists, epidemiologists, and experts in other relevant fields.

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Chapter 8

RANGE OF REGULATORY PROCESSES FOR SAFETY

Food safety regulation in the United States often is seen as a simple choice between banning a substance from use in food or permitting its entry into a relatively free market. This perception primarily reflects the reality of food safety regulation as articulated in the Federal Food, Drug, and Cosmetic Act. In theory, a wide range of regulatory mechanisms could be applied selectively to different types of food substances, but in practice, the availability of a wide range of mechanisms probably would require changes in the law. The available types of regulatory action, as well as problems in standard-setting and the need to examine individual substances, affect the flexibility of any system of food safety regulation

Purposes of Safety Regulation

Many federal agencies undertake regulation with safety as the primary objective. As examples, the Occupational Safety and Health Administration regulates the safety of the workplace, the Consumer Product Safety Commission acts to assure the safety of most types of products purchased by consumers, and the Environmental Protection Agency is responsible for air quality and the safety of pesticides and many other toxic substances. Other agencies regulate safety in certain areas (such as the Federal Aviation Administration and air travel) or perform economic regulation with some consideration for safety (such as the Civil Aeronautics Board and airline routes). The approaches and experiences of these various agencies provide a perspective for examining food safety policy—a perspective that was not available when most of the food safety provisions of the Federal Food, Drug, and Cosmetic Act were enacted.*

There are several purposes or arguments for safety regulation. These arguments constitute a rationale for a policy of government intervention, as opposed to a policy that allows the market to function freely while imposing tort liability on manufacturers whose negligence causes injury or death. Tort liability includes the legal obligation of wrongdoers to provide compensation to those they injure.

One argument is that consumers (or workers, travelers, inhabitants, or whoever comprises the protected group) lack adequate information to evaluate the risks of a particular product or activity. As examples, people who consume saccharin, or peanuts, or swordfish may lack an accurate awareness of the accompanying risks.

A second argument is that the consumer is imposing a "spillover" risk on other members of society. According to this line of reasoning, the consumer of a high-risk food, in accepting the risk of disease, is putting a family at risk of loss of its support, a group of workers at risk of losing comradeship, and taxpayers and fellow participants in a health insurance plan at risk of having to pay health care costs for one careless consumer.

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*A comparison of safety regulation across various federal agencies is contained in Appendix C.

Additional arguments support safety regulation. An industry that imposes a risk on people may be considered to have unequal bargaining power compared to the people at risk, so that individuals subject to the risk are not adequately compensated for it in the market. With time, the public may have come to expect safety through regulation, so that consumers assume that any food allowed to be sold must be safe. Advocates of safety regulation may assign government a "paternal" or expert role in freeing the public from deciding which risks are worth taking or in protecting special populations with limited or no capacity for decision-making, such as children or fetuses.

Finally, the nature of the risk may justify greater protection than that afforded by the usual practice of making those who impose unreasonable risks on others pay for the consequences of their action through tort liability. For example, because cancer usually has a latent period of many years and the etiology of most cancers is not understood and may be complex, no food manufacturer, however negligent, is ever likely to be proved in court to have caused cancer in anyone.

Regulatory Mechanisms

Four major types of regulatory strategies may be applied to foods or substances in foods. These strategies may be roughly categorized as banning, disseminating information, taxing, and restricting distribution.*

Bans, in the context of food safety, are orders not to use a certain substance commercially in or as food. A ban is the most severe regulatory mechanism, curtailing not only industry's right to produce a product but also consumer choice. Because the ban is the most intrusive method,

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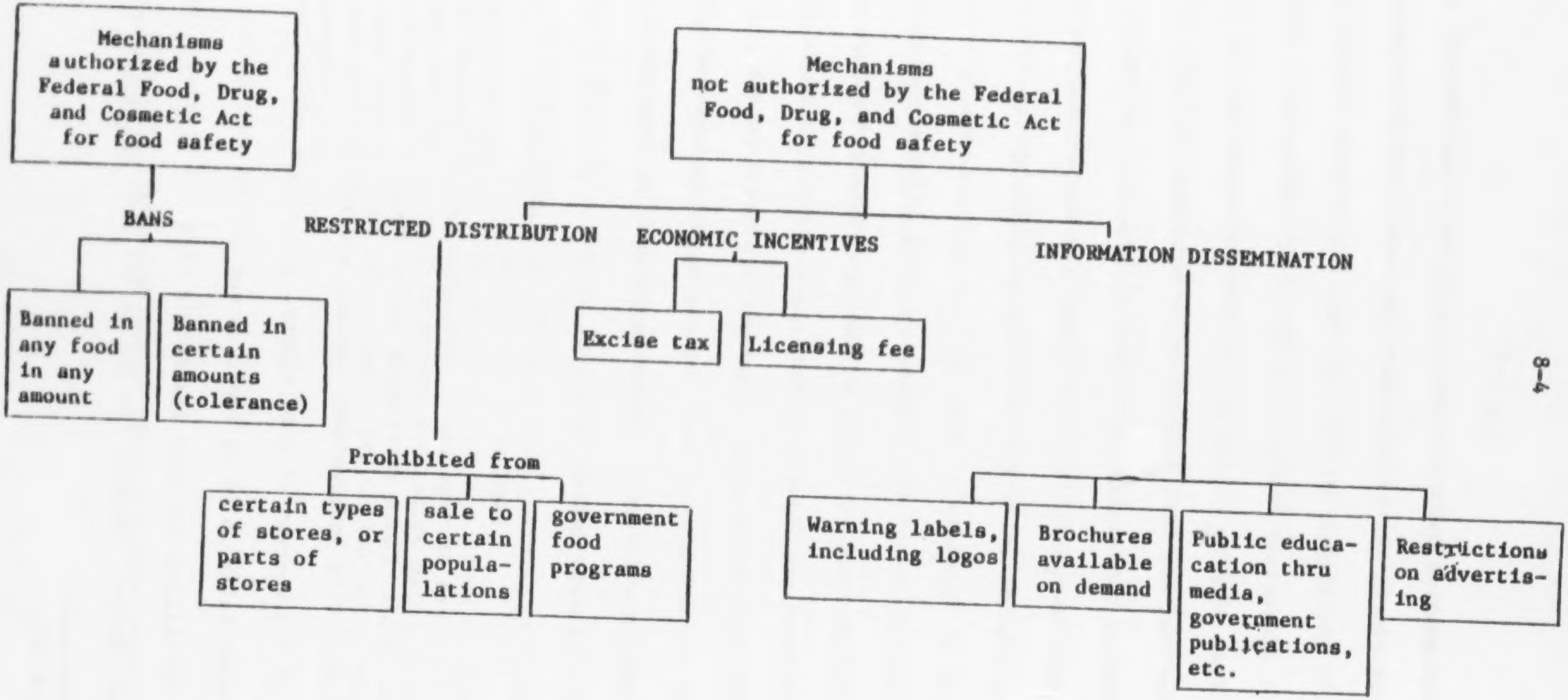
* See Figure 8-1.

Figure 8-1. Possible mechanisms of food safety regulation.*


Mechanisms authorized by the Federal Food, Drug, and Cosmetic Act for food safety
BANS
Banned in any food in any amount
Banned in certain amounts (tolerance)
Mechanisms not authorized by the Federal Food, Drug, and Cosmetic Act for food safety
RESTRICTED DISTRIBUTION
Prohibited from
certain types of stores, or parts of stores
sale to certain populations
government food programs
ECONOMIC INCENTIVES
Excise tax
Licensing fee
INFORMATION DISSEMINATION
Warning labels, including logos
Brochures available on demand
Public education thru media, government publications, etc.
Restrictions on advertising

*for explanation, see text

reasonableness requires that it be used only when less restrictive mechanisms are insufficient to protect health.

Currently, the law prescribes a ban for any "unsafe" food additive. Food substances that are not defined as additives face an easier test than additives in obtaining access to the market. Likewise, substances with a history of use have an apparent advantage over potential new substances in avoiding a ban.

Information dissemination may take several forms, including labeling. The purpose of this method is to help consumers make wise and informed choices. This process differs from a ban, since it places ultimate responsibility for food safety on the consumer rather than on a regulatory agency. But the choice of this method does not necessarily make the agency's job easier or simpler; the agency must decide, for example, whether a label should merely impart information or instead carry a clear warning, whether a label itself is sufficient or an accompanying informational campaign is necessary, whether the label should be directed at specific groups, carry a specific instruction, describe the evidence of risk, contain a symbol, be short or long, be worded strongly or mildly.

Forms of information dissemination other than labels include brochures that catalog the safety of different foods or food substances, signs in retail stores, informational advertising or printing of periodicals by the agency, and programs in schools or in other settings. As another strategy, advertising by producers might be limited, although this approach has difficulties. A regulatory agency could enact prohibitions on advertising certain products at all, on advertising them in broadcast media, on advertising them in the broadcast media at times when children are especially likely to be in the audience, or on advertising them without a warning message.

In general, the Federal Food, Drug, and Cosmetic Act as currently written does not explicitly authorize FDA to rely on information dissemination as a regulatory strategy. The agency does have some labeling and publicity authority, however.

Taxes are a rarely used substitute for other forms of safety regulation. But recently interest has increased in the possible use of tax-borne economic incentives that deter risk-taking and make producers or consumers pay the costs of the risks they generate. Taxes are applied to some hazardous products, including tobacco and alcohol, as a source of revenue. One strong reservation concerning the use of taxes as a means of promoting safety is that the tax burden may fall most heavily on the poor.

The last method of safety regulation involves restricting distribution of hazardous commodities, so that certain populations can obtain them only with difficulty. Examples of restricted distribution, either actual or possible, include prescription drugs, laws that forbid the sale of certain items to minors, prohibitions on the sale of a product in government food service programs or on government property, and bans on serving certain foods in school lunch programs or in nursing homes. A different type of example would be a requirement that certain foods be offered for sale only in certain kinds of stores or only in a separate part of a store. Another possibility is to prohibit restaurants from serving particular items, or to permit restaurants to serve such items only if they are identified.

The strategy of restricted distribution of foods is not now available to FDA. It involves questions of practicality, some of which are exemplified by the case of saccharin. For instance, is it possible in practice, without great expense in enforcement, to allow the sale of soft drinks containing saccharin to adults but not to children? Is it possible to permit the sale of saccharin for health purposes only to people who would benefit from it?

The purpose of a specific measure of safety regulation will help determine which regulatory method is most appropriate in a particular situation. In some cases, a program supplying adequate information to the public might appear sufficient. In cases where the purpose is to protect special populations, a policy of restricted distribution may be more appropriate. Sometimes it could be desirable to apply more than one regulatory method to a particular food hazard.

Problems in Setting Standards*

Safety regulation is accomplished largely through the setting of standards. In the food safety area, such standards could include general rules for determining the magnitude of acceptable risks, limitations on how much of a hazardous substance will be allowed in the diet, and other measures that bear on the level of risk.

Agencies set regulatory standards of safety through a process that combines health, economic, and political considerations and is partly formal and partly informal. Because of a number of problems in the setting of standards, this process may be unlikely to achieve precise and predictable results.

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* See Glossary, Appendix I, where the term "standard" is defined.

One problem that is ubiquitous in regulatory standard-setting is the uncertainty of information. Several chapters of this report (especially chapters 3, 5, and 6) describe difficulties in identifying and measuring health risks and benefits associated with food substances.

A second possible problem is the enforceability of standards. An agency may be inclined to compromise on an issue of safety if the procedural requirements of the statute for establishing or enforcing the agency's position are complex and burdensome. Also, the success of regulation depends heavily on industry compliance and the means to test for compliance. These factors may bias regulators toward the direction of standards that can be enforced easily.

A third problem in standard-setting is the effect of regulation on market competition. Compliance with regulation can be expensive and serve to protect large firms. Regulations sometimes have the effect of favoring some companies over others. Standards also can act to freeze existing technology, unless regulation has other technology-forcing aspects.

Finally, standards must be capable of surviving judicial review. Regulations can be challenged in court on the grounds that they violate statutes, are arbitrary or capricious, or were adopted without proper procedural safeguards. The need to prevent adverse judicial rulings forces agencies to adhere to formal procedures, whereby all interested parties have an opportunity to respond to every agency proposal. Standard-setting thus becomes cumbersome and lacks continuing informal, broad exchanges of views among interested parties and agency officials. Moreover, judicial review and regulatory proceedings are time-consuming, so that years can elapse before a proposed regulation takes effect.

These problems on the whole tend to discourage regulatory initiative. Established agencies adhere to familiar patterns; they try to avoid imaginative approaches that would have unpredictable results related to health risks and benefits, could create enforcement problems, might inhibit competition, and would engender lengthy and difficult litigation.

Sometimes these problems appear so great that agencies prefer reaching an informal, tacit accommodation with industry to establishing a formal adversarial relationship. The informal dimension of regulation may deserve emphasis. Agency proposals are published in the Federal Register in technical language and are subject to procedural safeguards, but agency officials may conduct deliberations and reach decisions informally. Agency priorities need not be established through formal rulemaking. In making decisions, agencies are likely to consider the effects of alternative regulatory policies on agency credibility with the public and Congress, on the economy, and on other concerns that may or may not be listed in the applicable statute as appropriate subjects of consideration.

Individualized Screening of Substances

Although there are advantages to setting broad or generic regulatory standards that are applied automatically to large classes of substances, some agencies find it necessary to evaluate substances individually to decide upon appropriate regulatory action. FDA regulation typically focuses on individual substances to determine whether they are safe enough to be marketed under proposed conditions. Beyond the usual problems in standard-setting, there are particular problems in screening that create obstacles to effective regulation.

A fundamental difficulty is that of devising meaningful tests for safety. Part of the regulatory screening process involves determining how much evidence is necessary to justify action and which tests are appropriate to generate evidence. The logistic and ethical problems of epidemiologic tests, the high cost and extrapolation problems associated with animal tests, and the newness and limitations of _in vitro_ tests have been discussed in Chapters 3 and 5.

The use of experts also presents difficulties to regulators who must make a decision about a particular substance. The most knowledgeable experts may have ties to industry and thus a potential conflict of interest. Few scientific experts feel comfortable making decisive judgments without better data than are usually available. The lack of dependable data may induce advisory committees, created to provide expertise, to issue reports that are worded so ambiguously as to aggravate confusion.

Consideration of benefits is a third area of difficulty. If regulatory decisions are made solely on the basis of risks, absurd or unacceptable results are possible; few people would argue that corn or fish should be subject to a ban if they present the same risk level as one of several similar chemical color additives. But the difficulties of measuring and comparing risks and benefits make pure risk-benefit analysis an improbable regulatory tool. To deny agencies the authority to consider benefits also may be impractical, because agency officials would find it difficult to resist considering the benefits of a substance before proposing to ban it or restrict its use, regardless of statutory criteria. Another aspect of benefit consideration is that benefits, like risks, may appear small on the societal level but great in the case of an individual, or vice-versa.

The distinction between new and established substances, or uses, poses another dilemma in individualized screening. Compared with substances already in use, the benefits of new substances are less likely to be known, but because new substances undergo extensive laboratory tests for safety, their risks are more likely to be known. Fewer people are inclined to urge the approval of new substances, because they are not attached to them from experience. This distinction has no clear bearing on the safety of the nation's food supply, except insofar as the introduction of increasing numbers of new chemicals into the environment could elevate, or reduce, the risk of cancer or other diseases. If a new or safer substance can substitute for an established one, or will provide significant health benefits in other ways, its use may be clearly desirable.

Special populations present another complication. Some populations, typically including pregnant women and children, may require special protection against risks. Other populations, such as members of a particular industry or inhabitants of a region that produces a food, may be excessively burdened by bans or other severe forms of regulation.

Framing a Flexible Policy

The approaches and problems mentioned in this chapter indicate the desirability of a flexible food safety policy.* The present study suggests that the policy should allow for technologic change in assessing risks and assessing benefits and should contain a built-in mechanism for evaluating the effects of regulations and adjusting them accordingly.

A flexible policy would apply the appropriate mechanism of regulation to a particular class of substances, would allocate regulatory resources to classes of substances in rough proportion to the risks they pose, and would discriminate among populations to the extent that is feasible. Most important of all, a flexible policy could accomplish a manifold objective: protecting the public from inordinate and undisclosed risks, while promoting technology that improves safety and preserving the advantages of consumer choice and fair competition. The committee's suggestions for the framework of a flexible food safety policy for the United States are presented in the next chapter.

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*This chapter summarizes a wide range of issues of safety regulation. For further discussion of these issues, see Stephen Breyer, "Analyzing Regulatory Failure: Mismatches, Less Restrictive Alternatives, and Reform," 92 Harvard Law Review 549 (1979); Peter Barton Hutt, "Safety

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Regulation in the Real World," 28 Food Drug Cosmetic Law Journal 460 (1973); and National Research Council, Committee on Principles of Decision Making for Regulating Chemicals in the Environment, Decision Making for Regulating Chemicals in the Environment (Washington, D.C.: National Academy of Sciences, 1975).

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Chapter 9

CURRENT POLICY ISSUES AND RECOMMENDATIONS

Need for Reform of Food Law

A series of episodes calling into question the safety of particular foods or their constituents, among them the cases noted in Chapter 3 of this report, has heightened public concern over federal regulation of food safety. In some conspicuous cases, there has been controversy over whether existing regulation is insufficient or excessive.

The problem is in part a consequence of the integration of advanced technology into modern society. Food production, processing, and distribution now separate the farmer from the ultimate consumer by a long chain of events over which consumers have little influence. Most persons have scant knowledge of the steps in food production. They must rely on a complex modern industry, including modern farming, to deliver an adequate supply of healthful and nutritious food, and a complex modern government to help safeguard the product for human consumption. Industry is constantly developing new products, and new ways of processing old products, for the public's diet. Few of these products have been shown to pose health hazards, but vigilance is required for those that do. Increasingly sensitive techniques have become available to identify and detect potentially harmful substances in foods. These techniques, however, do not eliminate many of the uncertainties in assessing health risks, particularly in relating laboratory findings to human risk.

To establish regulatory standards that protect public health, inspire public confidence, minimize interference with individual freedom of choice, and stay within the bounds of economic and political feasibility requires an integrated and widely comprehensible system of regulation.

With respect to these criteria, the present food-safety decision process has many shortcomings and inconsistencies. The system is confusing and cannot be presented to the public in any simple way. Few non-lawyers or non-experts know the difference between GRAS and non-GRAS, or between pre-1958 and post-1958 additives and non-additives or why chicken and non-poultry meat should be dealt with differently in respect to nitrite. As a result of this confusion it is difficult to get public support for the regulatory system, but opposition to seemingly arbitrary specific actions is readily mobilized.

Foods and food components are categorized by statute for regulatory purposes, but these categories are confusing because they lack a readily comprehensible ordering principle. Existing categories, such as GRAS or prior-sanctioned items, depend on dates, whether the substance is natural or synthetic, which foods contain the substance, and other factors (see Chapter 2). Cancer, in the Delaney clause, is treated separately from other kinds of health risks, but the clause applies only to some categories of foods and food components.

Further, the United States now has an absolute food law in theory but a system that does not consistently follow the law in practice. If the law permitted more latitude, better accountability on the part of regulatory agencies could be achieved. The system ostensibly does not provide for consideration of benefits, but in fact, the regulatory agency often takes benefits into account in making decisions. In P.L. 95-203, the Congress explicitly mandated that this study consider the weighing of benefits and risks in food safety regulation. The consideration of benefits should be explicitly acknowledged and provided for in any revised food law.

In what follows, the committee is not proposing an ideal food safety system but one that it hopes will eliminate or reduce many present problems. In dealing with a subject of such complexity, and which has generated much emotion, there are a number of approaches. Each has its adherents who can present reasonable arguments for their own scheme. The key issues on which differences of opinion exist are:

1. The degree to which food should be regulated differently from other matters of safety.

There are those who feel strongly that the public has become accustomed to security about the safety of food because of government action and that this security should be assured. Food is such a basic substance, and the issues of food safety are seen as so complicated and numerous that it is not reasonable to expect the average consumer to have to make choices, particularly where the risk is not immediate, is serious if it occurs, and may occur infrequently (for instance, bladder cancer). Those of this opinion have little confidence that available information strategies, such as logos and labeling, could provide sufficient information to allow consumers to make truly informed choices.

Government would be expected to take feasible necessary measures to assure maximum safety and the consumer would then have a minimum of choices regarding food safety. The Delaney clause exemplifies this point of view.

Others believe that consumer choice should be encouraged whenever the risk is not excessive. In this view, every effort should be made to provide appropriate information so that consumers can make informed choices, although it is recognized that information is not always used effectively. Because no single food item is essential for health, it can be argued that consumers should have maximum freedom to choose which foods they will eat, and to substitute some foods for others.

2. The amount of discretion that should be given to a regulatory agency.

There are those who believe that regulatory agencies should be given little freedom of decision in order to be resistant to outside efforts to influence decisions. Such efforts can result in excessive regulatory delays and interminable litigation. According to this view, there is also a tendency for the regulated industries to gain control of the regulatory process, and the more freedom the agency has, the more likely this is to happen.

Those of the opposing point of view accept the fact that regulatory agencies may be subject to this tendency, but emphasize that the intricate nature of the problem, the rapid changes occurring in science, and the need for prompt but discriminating action make it better to allow the agency to operate in the context of broad but well defined principles, while assuring greater participation of the public in agency considerations.

3. The relative values to be placed on risk and benefit.

There also is a difference of opinicn as to whether regulation should be based primarily on the estimation of risk, with benefit as a modifier, or on benefit, with risk as a modifier. Most systems of regulation of food safety start with the question of risk, because the purpose of regulation is to protect the public from harm. Benefits may be considered, if at all, to determine whether a substance with some risk might still be approved for use. In at least one country (Great Britain),* the system starts with a consideration of benefit and if none can be demonstrated the substance is not approved.

4. The use of risk/benefit analyses and the concept of "acceptable risk."

The idea of weighing risks and benefits to reach a clear-cut decision about a substance is appealing. This approach is proposed frequently. This report, however, supports the point of view that neither risks not benefits are always readily quantified and almost never can be expressed in commensurate units. Although risk/benefit analysis may be useful as an organized approach to assessment, no specific numerical ratio usually results from the process, and the end product is an estimate based on informed judgment.

The term "acceptable risk" has been called into question. This refers to a level of risk that most consumers would accept in order to secure real or perceived benefits. It is pointed out by some that the information available for an informed decision by most consumers is rarely adequate. Furthermore, the concept of "acceptable risk" has been criticized by those who feel that it may lead to complacency rather than to attempts to decrease the risk, even if the risk appears unavoidable at present.

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*See Appendix D.

5. The gradation of risk.

For regulatory purposes there are some who feel it would be desirable to categorize risks in ordinal or categorical terms; such a scheme is discussed in this report. However, inadequacy of the data by which risk is determined suggests to others that such categorization is not rigorous and can be misleading.

6. The special handling of the risk of cancer.

The existing law tends to give the risk of cancer special status and to regard any likelihood of its occurrence as unacceptable. This position has much support, because cancer is a catastrophic event for the individual victim, it is much feared by the general public, and there is doubt that a threshold of dosage exists below which carcinogens do not cause cancer. Many persons, nonetheless, knowingly increase their risk of cancer in order to enjoy the perceived benefits of activities such as cigarette smoking. Without necessarily singling out cancer, many would agree that chronic, irreversible, handicapping, or frequently fatal conditions present a greater risk than acute, potentially reversible conditions with a comparable fatality rate.

The committee deliberated extensively on these and other issues and recognizes that no scheme will suit everybody. The framework presented in this report is one the committee consensus suggests as able to eliminate many of the problems in the present system. The remainder of this chapter presents the important concepts that should underlie any food safety policy in the view of those who share in this consensus.*

Throughout, it is assumed that decisions will take into account the best available scientific findings. This assumption is made in full knowledge of the shortcomings of our present technology of assessment, but with an appreciation of the rapid progress in many relevant scientific disciplines and the prospect that more adequate scientific data can become available in the future to aid regulatory decisions.

General Characteristics of a System for Food Safety Regulation

A national food safety policy should encourage the establishment of reasonable goals for the reduction of risks of carcinogenic and other toxic substances in the food supply of the U.S. population. The policy should take into account the averages and the wide variations in food requirements, preferences, and exposures to particular foods in a heterogeneous society. The policy should maximize public health advantage while protecting individual choice, and foster a regulatory system that

- *is comprehensive in its application*
- *discriminates among risk levels*
- *exerts pressure to reduce the risk in the food supply*

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*See minority statement following Chapter 10.

- *allows a wide variety of regulatory and educational approaches*
- *focuses decision in the responsible judgment of legislators and accountable administrators, using the best scientific information and the fullest expression of informed public opinion*

These characteristics are elaborated below.

• The system should be comprehensive, applying to all foods and their constituents on a uniform and equitable basis. However, it must also take into account that particular foods or food constituents are not usually consumed in isolation but rather in combinations that vary both geographically and culturally with diverse diets.

• The system should discriminate among risk levels, and assign priorities among categories of risks,with emphasis on those that pose the greatest potential hazards. It should apply severe and general constraints only to items involving the greatest, most frequent, and most certain dangers. It should recognize that it is impossible to eliminate all risk. As a matter of feasibility, the regulatory process cannot be applied individually to each of the great number of substances in the human diet. The regulatory agency must have a way to set priorities, so that it can devote its efforts to those substances and combinations that represent the greatest risk, in terms of numbers of persons exposed and seriousness of outcome.

• Development must be encouraged for less risky substitutes for substances that have benefits but a significant degree of health risk. There should be continuous pressure for reduction in the overall risk that is permitted in the food supply. The perspective of the FDA should include the total food supply, rather than each food and each substance in isolation. Some substances interact synergistically to enhance their individual effect; furthermore people may be exposed to multiple small risks whose total effect, even if less than additive, may be substantial.

- The system should allow much greater variety of regulatory and educational approaches than is now possible, in order to deal with the extremely complex problem of food safety and to avoid imposing undue burdens on producer and consumer alike. It is not enough to identify some substances as hazards and ban them, while ignoring other substances possibly of equal or greater consequence. Some substances should be banned entirely, others should be made available only with certain restrictions or only to certain types of consumers, and still others should be distributed with appropriate warning.

- Regulatory discretion is required, because safety cannot be defined entirely by scientific processes or by objective judgments of experts. Scientific processes and expert judgment are aids in assessing the probability and extent of risk, and the probability and extent of some types of benefits. Nonetheless decisions must remain the province of responsible judgment by legislators, or by administrative agencies acting by delegated authority, regarding the degree of safety to be sought. The American people are properly cautious about delegating regulatory discretion. A reasonable amount of discretion, however, is the only way in a situation of such complexity to avoid a far more burdensome and less effective set of rigid prohibitions, because statutes cannot deal in infinite detail with all possible eventualities.

The Process of Regulatory Action

To translate these general characteristics into specific practice is not an easy task. The recommendations that follow should be regarded primarily as concepts and principles that may provide a basis for more detailed legislative considerations, rather than as strict prescriptions.

Given the complexity of safety issues and the rapid changes brought about continually by new technology, legislation must prescribe as explicitly as feasible the statutory basis for regulating substances, the overall standards by which the regulatory process should be governed, the general procedures to be followed by the agencies of administrative regulation, the manner in which consumers and industry should have access to and participate in the process, and the procedures for regulatory accountability to responsible executive authority and ultimately to the Congress.

A reasonably phased transition should be provided in changing from the existing system to the recommended comprehensive one, with appropriate targets for safety to be achieved cumulatively on a suitable schedule. The FDA should follow a planned and systematic process to guarantee that all major aspects of the complex problem are taken into account without bogging the agency down in excessively detailed consideration of lesser priority issues. The FDA will not be able to switch immediately from the present system to a more comprehensive and balanced approach. As the existing system is converted, FDA will need more adequate institutional arrangements for the provision of scientific advice (see Section 3d below) as well as for fuller public contribution. Added administrative discretion must be balanced in the careful drafting of statutory policy by constant appraisal of independent scientific experts and by the interested public, and by provision for continuing scrupulous review by responsible executive authority and the Congress.

1. Statutory basis

The Congress should revise the food safety provisions of the Federal Food, Drug and Cosmetic Act to abolish the differences in the statutory standards among categories of substances, and create a single standard for food safety regulation applicable to all food substances.

Such a change should make it possible for FDA to replace the substance-by-substance approach with a system that allocates regulatory efforts according to the magnitude and nature of risks and benefits.

2. The process of risk assessment

In addition to considering extent of risk, use of a particular substance, and severity of effect, the regulatory process must consider other relevant factors.

The process should ensure attention not only to the severity and frequency of the risk posed by particular substances, but also to such questions as these:

- Is there a satisfactory less risky substitute for a particular substance that poses risk?
- Is it possible to spread use over several alternatives and thereby to reduce any residual or uncertain risk?
- Can anything be done to accelerate the development of better substitutes?

- What are the economic and other social costs of the substance and of its possible substitutes?
- What benefits would be sacrificed if the substance were not available? Would such sacrifice add to the health risk, or impose major burdens of other types on the public?
- Do the risks and benefits affect the public generally, or apply differentially to specific groups--the young or aged, pregnant women, those with special health problems, those with limited income, and those with more or less capacity and opportunity to make use of substitutes or make rational decisions for themselves?

One orderly way to apply common sense and informed judgment to take into account these and other complexities is presented as a decision framework in Chapter 4. This illustrative framework is not a formula that can be applied with scientific precision, or calculated step by step as if it were a mathematical equation; it represents one way of proceeding in arriving at possible regulations governing individual substances. The process requires a substantial measure of administrative discretion and should not become a statutory straitjacket that invites debate and litigation at each stage of the process.

3. Components of the regulatory system

A statute permitting a comprehensive approach should define broadly the categories and degrees of risk, and should relate these to appropriate risk containment, the permissible type of regulatory activity, and the type of accountability to which regulation would be subject, by executive, legislative, and judicial review. The FDA should have statutory authority and resources to assess (with the help of the institutional arrangement for scientific advice proposed in section 3d below), the risk of all constituents in the food supply.

Degrees of risk can raraly be defined in numerical terms because of the complexity and constantly changing nature of the problem. Risk, as noted in Chapter 4, encompasses the probability that harm will occur, as well as the seriousness of the harmful effect. This report will not attempt to define risk categories with any precision. In arriving at risk categories, or sub-categories, the FDA will need to consider not only potency of the harmful substances, but the levels at which it is present in foods, the number and susceptibilities of people who consume the foods or food ingredients of concern, the amounts of such foods consumed by various segments of the population, and the type of health threat posed. A potent substance present in exceedingly low concentrations in some foods might not represent a health risk to consumers, but the same substance might be a hazard if it were present in other foods or in high concentration.

Categorizing substances by health risk will aid the regulatory agency in setting priorities so it can devote its efforts to areas of greatest concern. Certain kinds of harmful effects, such as irreversible effects and intergenerational effects, would be weighted very heavily. Even when these affect only a small portion of the population, or have a low probability of occurring, they would merit greater concern than would less serious effects that might occur with greater frequency. For instance, the equal probability of a mild allergic reaction and a carcinogenic effect call for rather different responses.

In order to act, a regulatory agency must take each item—for example, a particular food additive—and consider how to put it in some rank order, among the tremendous number and variety of others. For purposes of food regulation, this cannot be done by grading the items with precise numbers, on some linear scale, on the basis of scientific tests. This impossibility results not only from the uncertainty of some of our testing techniques, but also from the fact that various factors have to be taken into account—how probable an adverse effect may be, how severe the effect, how long it may take to develop, whether it affects everyone or only certain types of people, and whether its dangers may be averted by one or another type of prohibition, restriction, provision of alternative substances, or educational effort.

The problem is similar to those encountered in other contexts, such as the grading of meats (prime, choice, good) and the grading of students' performance (A,B,C,D,F). In cases such as these, the grader must consider many factors, not all of which are quantifiable along a single dimension. Furthermore, the boundaries between categories cannot be sharply defined.

Although the problem is complex, it seems necessary, in order to permit practical action, to authorize the Food and Drug Administration to assign each substance under review to one of a limited number of categories—three, for example—primarily on the basis of judgment about both degree and type of risk.

a. Categories of risk *Without suggesting precise statutory language, the committee proposes that the FDA should be authorized to* *act differently for several broadly defined risk categories, such as high, moderate, and low. These categories at present cannot be defined by precise quantitative scientific standards, but would depend on informed judgment. Their function would be to provide a rating scale to help determine regulatory response and priorities.*

The committee emphasizes that risk and response are frequently multidimensional, non-linear, and hard to define. Nonetheless, practical considerations make useful the designation of a small number of general categories that can be readily understood by consumers. Three categories might indicate high or serious risk, moderate or intermediate risk, low or slight risk. The number of categories and the names actually attached to them should be chosen to be easily recognized and understood by the general public. They also should convey some sense of how the consumer should respond to the warning--for example "Dangerous. Use only when necessary and as directed in attached information." Each of the major categories could be subdivided for practical purposes. For simplicity this report uses merely the relative designations "high," "moderate," and "low." The designations would be based both on the toxicity or potency of the substances and the estimated level of exposure of the general population or various special subpopulations. The boundaries between the categories would presumably be defined so as to leave some latitude for discretionary judgment.

High risk foods or ingredients are materials demonstrated by experience, or suitable scientific testing, to be likely to result in severe (irreversible, incapacitating, or lethal) damage to humans, either in general or in susceptible subpopulations, with appreciable frequency.*

Moderate risk foods or ingredients are materials that, as shown by experience or suitable scientific tests, may cause appreciable harm to humans, either in general or in susceptible subpopulations, with sufficient frequency to justify regulatory action designed to modify their use.

Low risk foods or ingredients are those for which there is evidence of some risk, but the risk is neither serious nor frequent enough for placement in the moderate risk category.

Other food Outside of these three risk categories would be food and food ingredients that, under current knowledge, individually neither pose known risk nor the presumption of any significant risk under reasonable patterns of consumption.

b. Response of regulatory system based on risk categories

Once the risk of a particular food or food substance has been established according to its potency and exposure level, and a risk category has been assigned, the optimal regulatory strategy must be selected. This should take into account not only the risk of continued use but the risk of limiting or discontinuing use.

In some cases, this may mean assessing the objective or perceived benefits so as to weigh them against risks. But, the range of regulatory options for a given risk category should be broad so that the option selected can be carefully matched to the particular case. In many instances an option lying betweeen total discontinuance of use and unrestricted use may be optimal either temporarily or indefinitely.

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*As an extreme example, food obtained in highly contaminated run-off waters from a mercury processing plant would be high risk for continuous consumption.

The committee suggests that standard symbols (as have been used to warn of poisonous or radioactive materials) for each risk category may be useful as a means to alert consumers of the need for further information. Such logos would require little space or cost. Depending upon the risk category, further information might be required to be attached to the product or made available on request by the distributor. Experimentation with such logos is necessary to establish their effectiveness.

The committee believes that, whether through logos or other means, consumers must be given the opportunity to play a larger role in food safety decisions. Further research on the most effective means of providing warning and information to consumers is urgently required.

High risk - Regardless of health or other benefits, FDA should be authorized to ban high risk substances from the food supply. A ban will be most appropriate when a satisfactory substitute for the high risk food or food ingredient is available. If no such substitute is available, and the risk is clearly outweighed in well defined circumstances by significant benefits that are not available from safer sources, the FDA should be authorized to permit marketing of such substances, through restricted channels or with appropriate labeling, for limited purposes, to limited categories of the population, or under other restrictions. Such high risk but essential foods or ingredients could be identified with a conspicuous and distinctive high risk logo, requiring an attached circular outlining the nature of the risk and the prescribed appropriate use. The number of high risk substances made available for such restricted distribution would be expected to be small. (Item 5 discusses accountability.)

Moderate risk - If moderate risk foods are to be marketed, they could be required to display a conspicuous distinctive logo, designed uniformly to identify clearly the moderate risk category for all purchasers. If foods or ingredients involving moderate risk have suitable alternatives or offer no significant health benefits, FDA should be authorized to exercise discretion to deter their use by means* that could include restricted distribution, financial disincentives, or outright ban. Purchasers of moderate risk foods should be provided by sellers, on request, with a descriptive circular explaining the risk entailed and special precautions to be taken in consuming the particular food.

Low risk - Low risk foods should be exempt from special regulatory control, but not necessarily from educational efforts to reduce the risk still further by acquainting the public with the risks they may pose, particularly in combination with other substances.

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*See Chapter 8.

General reduction of risk - Besides devoting its efforts to circumstances of greatest risk, FDA should take other effective actions to reduce risks where desirable. It should set tolerance levels that encourage or require efforts to develop new technologies to reduce risks. Such technology-forcing tolerance levels could focus on reducing the amount of risky substances in a food, or in seeking substitutes for the risky food or ingredient.

c. The consideration of benefits *When benefits can be estimated or objectively assessed so as to assist the judgment of the consumer and of the agency, FDA should be responsible for obtaining such assessment. However, it should continue primarily to be risk that triggers government intervention in the food supply, and the government must remain cognizant of the centrality of risks in food safety regulation.*

The Congress has not specifically authorized FDA to establish categories of risk or in general to take into account the benefits of substances in making regulatory decisions.* The mandate of the Saccharin Study and Labeling Act (P.L. 95-203), requiring recommendations with respect to the weighing of benefits against risks, indicates congressional desire to deal explicitly with a problem that has not been faced satisfactorily in the past.

As difficult as it is to get an authoritative assessment of risks, it is often still more difficult to make a precise estimate of aggregated benefits that may include components that are physiologically, psychologically, or economically defined. Physiological health benefits are sometimes easier to measure than other types of benefits, but any complete risk and benefit assessment presumably should include all benefits.

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*See Chapter 2.

From an economic perspective, people buy food products because they perceive a benefit in them. But economic gains, like matters of aesthetics and pleasure, are frequently extremely difficult to measure and evaluate. Given the present state of the art, they can be estimated and compared only very crudely.

In a few, unusual cases, FDA may find that high risk foods or substances may have offsetting benefits of such importance, especially for specific segments of the population, that their distribution through special channels should be permitted, at least for special purposes. Under those unusual circumstances, such high risk foods or substances could be accompanied by a logo and circular as described earlier in 3b. (Item 5 discusses accountability.)

d. Scientific testing, research and advice *The regulatory process must incorporate contemporary science and technology as its most reliable source of information. Regulatory agencies, therefore, must have access to scientific and technologic expert services that will actively seek out the information required for the regulatory process.*

The committee favors the view that new institutional arrangements should be developed to provide augmented research services rather than relying primarily on improving present research efforts that are scattered in individual agencies. Any such new institution should be confined to the objective and scientific assessment of health risks and health benefits, *leaving policy judgments that may involve other considerations to the responsible administrative agency.*

The committee emphasizes that its recommended approach to food safety regulation would, by favoring broader regulatory options than simply to ban or to ignore, promote research efforts to improve assessment of risks, to find more effective and safer food constituents and to heighten public awareness of the importance of effective food safety choices. The committee believes that FDA should be given appropriate discretionary authority to regulate within broad categories of risk for food safety. This should be accompanied by a requirement, whenever possible, to obtain independent scientific assessment of the carcinogenic or other toxic dangers of the substances in question. Measurable and relevant benefits should be taken into account.

The regulatory process must incorporate contemporary science and technology as its most reliable source of information, especially since rapid changes in scientific knowledge and procedures may enhance recognition of previously unknown risks or benefits. This incorporation of information cannot be merely a passive process, since much information essential for sound regulation does not normally flow from theoretical science or from science and technology applied to meet other objectives. Regulatory processes need specific kinds of data that will not necessarily be developed for other purposes, and the agencies, therefore, must actively seek out the data required for the regulatory process. This requires both the capability for analysis of existing data and the ability to stimulate generation of new data through additional research, by whatever mechanism appears most appropriate.

The question of how to enhance the capability of the Food and Drug Administration and other agencies so that they may better deal with scientific questions of food safety regulation is an issue complex and important enough to warrant continued special study before a final decision is made. Keeping in mind the problems that have occurred when regulatory agencies carry out their own scientific research, several options have been discussed that are not necessarily mutually exclusive. Each regulatory agency concerned may need to provide some additional scientific capability within its own staff. It is probable, however, that the total food safety regulatory system would be strengthened if responsibility were to be assigned to some central testing group, whether established as an independent governmental agency or as a separate unit within a department with primary regulatory responsibility. Such a central testing group might also be set up under contractual agreement with a private institution, either a not-for-profit scientific institution, or a licensed and supervised commercial laboratory.

The committee favors the view that new institutional arrangements should be developed to provide augmented research services rather than to rely entirely on improving the present scattered efforts. Whatever arrangement is made, however, it must ensure that scientific competence of high order will be brought to the task, that all available scientific evidence will be carefully considered with respect to each problem under review, and that the scientific findings will be carefully considered in the process of final regulatory decision.

Any such new institution should confine its role to the objective and scientific assessment of health risks and health benefits, leaving the policy judgments and decisions on regulatory action to the responsible administrative agency. To assure adequate consideration, assessment reports should be public documents, available equally to all parties. This procedure would provide opportunity for the private interests affected, as well as the appropriate authorities in the Congress and the Executive Branch, to review the rationale for discretionary judgments to be made by the regulatory agencies. The scientific reports should of course include consideration of relevant data and information brought forward by consumer, industrial or other research groups.

e. Interim regulatory actions *Provision should be made for authorizing interim regulatory actions for substances of uncertain degree of risk, for a specified period of time. After more thorough testing FDA should assign the substance to an appropriate risk category and take appropriate regulatory action.*

In view of the rapidity of technologic change affecting the decisions on food safety regulation, the committee believes that provision should be made for authorizing interim regulatory actions. Whenever, on the basis of scientific evidence, it seems clear that adequate information to make a confident regulatory decision is not available, and in the absence of very great benefits associated with a particular substance, the regulatory approach should be conservative in its care to protect the public against possible risks. In such circumstances the FDA should be authorized temporarily to place a substance in the moderate or high risk category until available evidence justifies its reclassification. It may be appropriate to require that some substances be available for a limited time, e.g., 3 to 5 years, only for limited distribution to meet pressing needs for which low-risk alternatives are not available.

After more thorough testing, the FDA should assign the substance to an appropriate non-interim risk category and take appropriate regulatory action.

f. Flexibility, feedback, and evaluation *The regulatory structure must be flexible and able to respond both to rapid technologic change and to altered public attitudes. Furthermore, regulations also need built-in mechanisms for evaluating how well decisions achieve the intended results, and the degree to which decisions generate unintended, adverse or beneficial results.*

Available information may change and action that seemed best at a given time may be inappropriate later. As examples, analytical methods of detecting risks may improve, substitutes for potentially hazardous substances may be developed, and advances in predicting causes of disease may occur. The regulatory process must incorporate methods for responding to such changes.

g. Implementation *Regulations should be reasonable in terms of compliance, and enforceable.*

They must clearly spell out what is required so that regulated groups will know what is expected and be able to comply. The cost of enforcement must be commensurable with the risk that the regulation addresses.

4. Education and participation of non-government groups

The FDA and other regulatory agencies should be encouraged to use campaigns of public education to increase public understanding of safe and nutritious diets. Non-governmental groups should have ample opportunity to make their views known to those with responsibility for decisions. Advisory committees representing consumer, producer, and professional scientific groups should be permitted to review scientific reports that form part of the basis for decisions at the same time the FDA considers the information.

In an open society the safety and nutritional quality of the diet may be expected to be determined more by the understanding and desires of the public in general than by the sum of regulatory action that government may appropriately take. Successful efforts to educate the public with respect to the specific risks and benefits of various types of foods will make less necessary the imposition of onerous governmental controls and could greatly lighten the burden on the FDA and other regulatory agencies. Therefore, the FDA and other regulatory agencies should be encouraged to make use of campaigns of public information to provide warnings to consumers through labeling and similar measures, to promote effective consumer choice, and to develop broader informational approaches to increase public understanding of safe and nutritious diets. Such educational strategies should include more complete food labeling so that people with food allergies or diet restrictions can avoid those ingredients that are health compromising.

In the broadest sense, public participation in the regulatory process involves the expression of views by individuals and non-governmental groups of all kinds--consumers, industry, scientists, and others. The voluntary participation of these non-governmental groups can do much to avoid the necessity for coercive governmental regulation. If federal programs do not reassure consumer groups about the safety of the public food supply, and do not stimulate private business to eliminate or lower the risks in the foods on the market, the problem of enforcing regulatory standards will become far more difficult. Much may be gained by provision of opportunities for representatives of producer and consumer groups to come to agreement regarding the standards to be maintained on a voluntary basis, and by encouraging informal communication among interested parties. In the process, the groups have opportunity to present their opinions and to satisfy themselves as to the adequacy and fairness of FDA standards of safety.

The staff of the FDA and of the institutions providing scientific testing and advice should have increased opportunity for scientific contacts with scientists in other institutions. Such informal contact is the most certain way to keep abreast of the newest scientific developments, and to promote the free exchange of new information that will greatly benefit all interested parties.

The work of the scientific testing machinery may raise substantial issues about the safety of particular foods. Reports so generated, which are considered in making decisions, may appropriately be reviewed formally by advisory committees representing consumer, producer, and professional scientific groups, while the FDA itself considers the information. In addition, the formal procedure involving notice of hearing before final regulations are issued also provides official opportunity to interested groups to present their views. The effectiveness of all such formal procedures will be greatly enhanced by encouraging and facilitating communications among the various groups.

5. Accountability and jurisdiction

a. *The committee recommends that if the FDA permits the marketing of substances of high risk for limited purposes to subpopulations, with appropriate labeling (as explained in 3b and 3c), it should be required to report its decision in advance to the Secretary of HEW and through the Secretary to the appropriate committees of the Congress.*

Public participation involves the reaction of the voters in vesting authority in those political leaders who are expected to represent their opinions. This requires a relationship of accountability between full-time public officials, acting on the basis of advice from expert consultants, and their responsible executive superiors and ultimately the Congress. It is accordingly important to consider not only procedures for consultations with those outside the government, but to make sure that adequate procedures are established for accountability within the constitutional system.

Under the Federal Food, Drug, and Cosmetic Act, food safety authority is vested in the Secretary of Health, Education, and Welfare. The Secretary has delegated authority to implement the Act to the Commissioner of the FDA. When controversies arise, congressional committees often hold hearings to inquire into the impact and rationale of FDA decisions.

Under any regulatory system, either the present one or the one recommended in this chapter, at times decisions have to be made on the basis of discretionary judgment. In some cases of a most difficult nature, advance notice to the Secretary and to the Congress may be desirable. But, in the committee's view, the regulatory process will be best served in the long term by regular general review by, the Congress and Secretary of the agency's processes and performance, rather than by case-by-case approval of specific rulings.

b. *Attempts should be made to eliminate problems of overlapping jurisdiction among federal agencies concerned with food safety regulation. With respect to actions or failures to act on the part of other federal agencies that have responsibility for regulating substances in the food supply that may pose high or moderate risk, the FDA should be authorized to report the matter to the Secretary of HEW.*

Decisions affecting the safety of food are, of course, made not only by the FDA but by other federal agencies, notably the Environmental Protection Agency and the Department of Agriculture. These agencies share information and opinions informally and also through the Interagency Regulatory Liaison Group which was formally established to develop consistent regulatory policy. Interdepartmental committees of this type are not always effective in taking vigorous action, however useful they may be in informal cooperation.

A more effective way of managing the problem of overlapping food safety jurisdiction among federal agencies might include consolidating such jurisdiction. The Executive Office of the President, including such agencies as the Domestic Policy Staff, the Office of Management and Budget, and the Office of Science and Technology Policy, could, in the short term, help settle individual cases of overlapping jurisdiction and in the long term could study ways of ultimately eliminating the broader problem. In order to avoid the subordination of the members of the Cabinet to presidential staff agencies, these agencies should not be given the statutory power of decision, and their specific assignments should be left to the President's determination.

Until a long-term solution is found, the committee suggests that, with respect to any action or failure to act on the part of any federal agency responsible for regulating substances in the food supply that may pose high or moderate risk, the Food and Drug Administration be required to act as follows: after receiving the advice of the scientific advisory mechanism proposed above on the issue, to report the matter to the Secretary of HEW . Such report should also be made available to the appropriate congressional committees. Such requirement for these infrequent instances could be imposed by executive instruction, without the procedural complications that would be involved in a statutory mandate.

6. Strengthening the regulatory agency

The importance of FDA's mission demands that it be given the opportunity to employ the most competent staff possible, and to adopt the most effective system of administration. Among its other and more specific recommendations, this committee would give very high priority to this general one.

The committee recognizes that the kind of food safety system it proposes would involve somewhat greater delegation to the FDA than does, in theory, the present system. Such a system would require the FDA to make explicit and public determinations regarding degrees of risks, and to acknowledge the judgment that it now occasionally exercises tacitly to take certain types of benefits into account in its regulatory decisions. And, if these recommendations were followed, FDA would do both in the light of a public assessment of the risks and benefits of each important substance by an independent scientific institution, under the continuous scrutiny of the Congress and the public.

Under such a new system, the Food and Drug Administration would presumably need to be strengthened considerably in its professional component and in the effectiveness of its organization in order to meet the demands of a higher degree of delegation. On the other hand, the present system, while it may make it harder to detect deficiencies in the FDA's performance, does not permit the agency to make rational and balanced judgments as it selects one item for regulation and ignores another one. The importance of the agency's mission demands that it be given the opportunity and budget to employ the most competent staff possible, and to adopt the most effective system of administration. This committee, among its other and more specific recommendations, would give very high priority to this general recommendation.

Conclusion

If the assessment of risks and benefits of each food substance were subject to precise scientific calculation, the process of regulation would fit a more satisfactory pattern. Analysts could make observations and calculations based on the objective facts and put a number or rating on the balance of risks and benefits for each substance. Congress could then by law make the value judgment required and define the cutoff point for unacceptable risk.

But, even aside from the inevitable pressures arising from differences of opinion among producer and consumer groups, such a neat procedure is made impossible by the nature of the scientific process and by practical constraints. With respect to many substances, analysts cannot determine with precision the degree of risk involved, and are even more uncertain in the assessment of benefits. Moreover, there is great variation in both risks and benefits among various population groups.

Accordingly, if this committee were called on to make a recommendation on each particular food substance, it would be in great difficulty. The majority of its members, who are scientists, would find it difficult to move from a high measure of agreement on the objective scientific aspects of the general problem to a similar consensus on a particular policy decision. In fact they might differ on policy decisions as much as other citizens. The policy decision, which necessarily involves considerations that are not only scientific, must be made by an authority with the legal responsibility for such decision, seeking to take all considerations into account, i.e., by enactment of the Congress or by some administrative body to which Congress may delegate the duty.

The committee believes that Congress has an opportunity to develop an improved system of food safety regulation that will incorporate current scientific realities, and to exercise comprehensive control over basic policies and standards. This report's recommendation for the enactment of a new statutory basis of regulation, abolishing the irrelevant and impractical distinctions that now confuse the public and impede rational decisions, is in that desirable direction.

In the view of the committee, the recommended changes would not politicize, in the undesirable sense of that word, the present system. On the contrary, the proposed system would tend to take issues out of the realm of current controversy, dominated by confrontation between producer and consumer groups—thereby reducing conflicting pressures on congressional committees and their staffs. Regulatory decisions could be made on a more rational basis, and could be subject to more effective accountability to the Congress and the courts, than under the present system.

Chapter 10

OPTIONS FOR REGULATING SACCHARIN IN THE CONTEXT OF THE RECOMMENDATIONS IN CHAPTER 9

The committee believes that if Congress takes no further action on saccharin, it will be banned under present law by the Food and Drug Administration.* The committee further believes, as stated in Chapter 9, that Congress should modify the existing policy for food additive regulation. Were the policy modified along the lines suggested in this report, the FDA could deal with the saccharin issue on a more discriminating basis with a wider range of available options. If, however, the policy is not so modified, Congress has the alternative to deal with saccharin as a special issue by legislative enactment. Under these circumstances the committee sees a series of options, any of which might be chosen, in the light of the facts on saccharin presented in Part 1 of this report. 2/ These facts may be summarized as follows:

1. In rats, saccharin is a carcinogen of low potency relative to other carcinogens (doses necessary for effectiveness

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*FDA announced its proposal to ban the use of saccharin as a food additive on April 15, 1977 in the Federal Register. The proposed rule would ban the use of saccharin as an ingredient in packaged foods, including soft drinks, and as a table top non-nutritive sweetener. But, on an interim basis, the proposal would permit the use of table top sweeteners containing saccharin while applications to approve saccharin as an over-the-counter drug are considered. The proposed rule also would ban the use of saccharin in cosmetics that are ingested, including dentifrices, mouthwash, and lipstick. Use in animal drugs and animal feeds also would be prohibited. 1/ There has been no indication that FDA has changed its view on the use of saccharin generally; it is not entirely clear, however, what the agency intends to do about the minor uses of saccharin such as in cosmetics and as a flavor in drugs.

were high and produced approximately 30 percent incidence of bladder cancer in male rats).

2. In addition to acting by itself, saccharin promotes the cancer-causing effects of some other carcinogenic compounds in appropriate test systems.
3. Most likely saccharin alone, not the associated impurities, is responsible for these adverse effects.
4. Whether as an initiator or promoter, saccharin is a potential carcinogen in humans, but one of currently uncertain consequence and potency in comparison with other carcinogens. In any case, the large number of persons exposed to saccharin justifies serious continued public health concern.
5. Extrapolation from available animal data does not permit confident estimation of the quantitative effect of consumption on human cancer incidence. Current epidemiologic data are likewise inadequate for such estimation.
6. Available scientific data on possible health benefits of saccharin do not provide a useful assessment. Its potential benefits may include management of diabetes, obesity, hypertriglyceridemia, and prevention of tooth decay. The committee accepts the premise that the proper use of non-nutritive sweeteners in drugs and dentifrices presents slight risks and involves possible benefits.
7. Although psychological benefits of the use of saccharin and other non-nutritive sweeteners cannot be evaluated at this

time, it is evident that some persons perceive saccharin to be desirable and beneficial.

8. The observation that saccharin use among young children may be increasing suggests that public health officials should take a prudent course of action. There has been insufficient time for the possible effects of this greater consumption to be manifest, taking into account the generally long latent period between exposure to a carcinogen and its manifestation as cancer and the recently recognized promoter effect of saccharin in laboratory tests.

If Congress should choose to act on saccharin independently of general policy reform, the committee recognizes the following major options ranging from total discontinuance to unrestricted use. In response to the request of the Congress, a full set of options is provided, recognizing that some will not be favored.*

1. *Totally ban saccharin for human consumption in any form.* The rationale would be that there is reliable animal evidence to suggest that the number of cases of human bladder cancer may increase by an unknown number if saccharin consumption continues at present levels. There is not equally reliable evidence of compensating benefits. The anticipated consequences of a total ban would be: 1) no possible increment of bladder cancer due to saccharin; 2) less palatable dentifrices and less palatable, stable and convenient drugs; 3) return to nutritive sweeteners by an unknown number of persons with uncertain

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*Appendix G contains a document that the committee used in drafting Options 1 through 8.

effects on weight and health. Estimates of consequences would be markedly altered if an alternative non-nutritive sweetener were approved for use, or if other compensating measures, such as an educational campaign on the problems of obesity, were effectively implemented.

2. *Ban saccharin except for use in drug formulations and dentifrices.* The rationale would be recognition that the amount of saccharin consumed in these uses is so small that its contribution to risk is probably negligible. Consequences, therefore, would remain essentially the same as in (1) except for the benefits of more palatable dentifrices and more palatable, stable and convenient drug formulations.

3. *Ban saccharin except as in (2) and also classify saccharin as a drug.* If approved as a drug by FDA, saccharin might be distributed over-the-counter or by prescription but could not be added to foods during processing. If distributed over-the-counter it could be sold in bulk and added to foods by consumers as a "table-top sweetener." If distributed by prescription its use would theoretically be limited to those having specific medical need. Distribution over-the-counter would significantly modify the consequences described under (1) in the direction of somewhat greater risk to all segments of the population. The rationale would be that persons who desired saccharin would have access to it, but this option would tend to discourage casual use. Distribution by prescription would restrict the greater risk to medically-indicated segments of the population where there

is also perceived compensating benefit. Either course probably would significantly reduce saccharin consumption by eliminating saccharin incorporated into casually consumed "diet" products.

4. *Permit saccharin use as a consumer-added (table-top) sweetener, but not as a food component.* In this case, the rationale and consequences might be similar to those listed in (3) for an over-the-counter drug, but saccharin would not need to qualify legally as a drug.
5. *Without banning saccharin, seek to reduce both its general use and especially its use by groups that may be especially sensitive (males of all ages, pregnant women, young children).* This might be accomplished through product labeling, general education and/or restriction of distribution channels. For example, children would be less exposed if sales were prohibited in school cafeterias, vending machines, and to minors in general. This option could direct saccharin-containing products towards those for whom risks appear smallest and benefit greatest, and discourage use by those who might be at greatest risk.
6. *Extend current procedure under the Saccharin Study and Labeling Act which allows general distribution but with general warning labels.* The rationale would be that there has been insufficient opportunity for the Congress to consider adequately the new recommendations made in this report in answer to their request.

7. *Provide a special program for warning specific elements of the population of their possible risk.* For example, the label could warn "Not to be taken by pregnant women." It might also warn those who use saccharin to discontinue use at suitable intervals, so that residual saccharin can be eliminated from their bodies. (See 2/).
8. *Saccharin might be freely allowed, with no special labeling.* The possible consequences can be inferred from the Panel I report.

Summarizing, the options for limiting saccharin use include 1) banning of saccharin as a food additive; 2) permitting it as a sweetener only for certain uses, such as in dentifrices; and 3) permitting it also for use as a drug, if it should meet other requirements for drug use. In addition, Congress might restrict saccharin's use or distribution in various ways, and/or insist on various types of information or educational methods to discourage its consumption.

All committee members believe it desirable for the FDA to take steps to educate users as to saccharin's risks, and to further encourage the search for alternative non-nutritive sweeteners, some of which is already going on. As a whole, the committee does not see consideration of saccharin as an individual item by Congress as either efficient or likely to contribute to sound general policy. Most members of the committee believe that a total, immediate ban of saccharin would not be a sound regulatory step at the present time, nor do they favor Option 8. However, beyond agreement on these points the members hold a broad spectrum of views regarding which action they believe the FDA should take in regulating saccharin. Some members favor the existing FDA position, stated on page 10-1, under which saccharin would be banned as an ingredient in packaged goods, but would be permitted as a table top sweetener on an interim basis. Some members would limit its availability to sub-groups of the population, forbidding its use in certain products, such as soft drinks sold to children, or restricting its sale so that it would be treated as a drug, available either over-the-counter or by prescription. Other members believe that saccharin should be allowed to be marketed freely, subject to appropriate labeling. Still others would put it in an interim category pending further investigation of the potential benefits, and encourage efforts to minimize the amount of saccharin needed to achieve any given level of sweetness.

Under the general food safety policy and risk categories proposed in this report, saccharin could belong in either the moderate or high risk category, depending upon the discretion of the FDA. In assigning saccharin to a risk category, major considerations are: saccharin is an animal carcinogen (albeit of low potency), and cancers are irreversible and usually serious; saccharin is widely used, therefore human exposure is extensive. The irreversible nature and severity of the risk and the extent of human exposure suggest that saccharin be placed in either the moderate or high risk category. The judgment would be influenced by saccharin's apparent low potency as a carcinogen. Whichever category saccharin were assigned to, the regulatory agency would have the option of allowing continued use under specified circumstances. If saccharin were judged to be of high risk, the FDA would have the option of banning its use in whole or in part. If not banned, saccharin and all foods to which it is added could be identified by a distinctive logo for the appropriate level of risk, and fully explanatory circulars would be required to be attached or provided on request, depending on the risk level chosen. FDA would also be authorized to take other actions to assure that consumers are alerted to the estimated hazards of saccharin so as to encourage reduced consumption both generally and especially by subpopulations at particular risk. At the same time, those who especially want and need a non-nutritive sweetener and regard the benefit to them as greater than the risk would still have access to saccharin. Accompanying these steps, research would be encouraged to improve the assessment of both risk and benefit of saccharin, to develop alternatives, and to conduct prospective epidemiolqgic studies that might in time reduce uncertainty about the consequences of saccharin use. These steps might lead, at the discretion of FDA, to a gradual phasing out of saccharin use over, for example, a three to five-year period.

References

1. 42 Fed. Reg. 19996 (April 15, 1977).

2. National Research Council/Institute of Medicine. Committee for a Study on Saccharin and Food Safety Policy. Saccharin: Technical Assessment of Risks and Benefits. Washington, D.C.: National Academy of Sciences, 1978.

MINORITY STATEMENT

This statement was drafted by Fred P. Abramson (Panel I) and Joyce McCann (Panel I) in consultation with T. Colin Campbell (Panel II) and Sheldon Samuels (Panel I). It was circulated to the committee and panels (37 members). Helen Nelson (Panel II) concurred in full. Charles C. Brown (Panel I) and Beverly Winikoff (Panel II) agreed with parts of the statement. These are so indicated at the end of the statement. A comment on the statement by Charles C. Brown (Panel I) is included.

MINORITY STATEMENT

January 31, 1979

Fred P. Abramson (Panel I)
T. Colin Campbell (Panel II)
Joyce McCann (Panel I)

Helen E. Nelson (Panel II)
Sheldon W. Samuels (Panel I)

The following points represent those major areas of disagreement with Panel II's report. The first six deal with food safety policy in general; the last two deal with saccharin specifically.

I. CLASSIFICATION OF FOOD ADDITIVES INTO RISK CATEGORIES SUCH AS HIGH OR MODERATE FOR REGULATORY PURPOSES CANNOT BE DONE USING CURRENT SCIENTIFIC DATA AND THEORIES

There is no scientifically defensible way to divide carcinogens or other irreversible toxins into different risk categories. This was the conclusion of Panel I's report on saccharin, and is the predominant scientific opinion for carcinogens in general. The ability of science to quantify human risk has not advanced sufficiently since the formulation of the Delaney Amendment to permit the construction of a scientific rationale for such a scheme. Massive post facto human epidemiological experiments lasting for at least a full generation might accurately assess toxic risks in a quantitative fashion. Otherwise, we can only determine the qualitative potential for human risk. Having reached that judgement, we have reached the limits of scientific knowledge. An appropriate use of a categorization scheme is to prioritize possible hazards for additional studies.

II. IRREVERSIBLE TOXICITIES ARE DESERVING OF SPECIAL REGULATIONS

The characteristics of a regulatory system for compounds causing irreversible toxicities, frequently highlighted by cancer, should be distinguished from the characteristics of a system for compounds causing lesser and reversible toxicities. A single policy which fails to separate these two widely different consequences is dangerous and unrealistic.

III. RISKS FROM FOODS SHOULD BE LOWER THAN OTHER TYPES OF RISKS

The public has a right to food that is as free of serious health hazards as possible. The exposure group is enormous and the mode of exposure is by chronic ingestion—the optimal way for carcinogenesis. Applications of standards for occupational health, or comparison of food risks to risks from other sources is improper.

IV. DIRECT FOOD ADDITIVES SHOULD BE REGULATED DIFFERENTLY THAN OTHER CLASSES OF FOOD ADDITIVES OR CONTAMINANTS

The obvious reason is that it is easier to do something about a hazardous substance that is purposely added to food than it is to do something about a substance, whether natural or unnatural, which is already in food. Removing the class distinctions between GRAS, prior sanction, etc., for direct additives is sensible, but the ability to act on the readily removed substances should not be complicated by grouping unlike classes of additives. Certainly, in the ultimate control of cancer, one wants to pinpoint the most important sources of hazard, and it is clear that some of these may be natural substances in food. However, it is not clear that this is the role of the FDA.

V. A FOOD SAFETY POLICY SHOULD INVOLVE LITTLE AGENCY DISCRETION

The FDA has taken many actions in areas of food safety which indicate the tremendous pressures and complexities generated in the present decision-making process. It is hard to imagine that a policy which contains so few specific guidelines as that contained in the report could be a step forward. The proposed ability to consider benefits, while an attractive idea, is so vague that it appears to offset risks by unquantified benefits. The relative simplicities of our current food safety policy cannot be tampered with because the structure of which it is a part can only support regulatory decisions no more complicated than a stop sign on the street corner.

VI. A COMPARISON OF THE ISSUES RAISED IN THE CASE STUDIES IN CHAPTER THREE WITH THE RECOMMENDED POLICIES IN CHAPTER NINE POINT OUT THE WEAKNESS OF THE PROPOSED SYSTEM

The four case studies presented--saccharin, nitrite, mercury and aflatoxin--were selected because each presents important problems which should be taken into account in directing food safety. The report is so non-specific that one cannot, with the possible exception of saccharin, deduce from it how these substances should be regulated.

Alternative Recommendations for Saccharin

VII. THERE IS LITTLE REASON TO POSTPONE A DECISION ON SACCHARIN UNTIL THE ONGOING EPIDEMIOLOGY STUDIES ARE COMPLETED

An examination of present day bladder cancer cases represents saccharin ingestion at much lower doses than the current dose, especially when the younger age of current saccharin users and the singular availability of saccharin as a non-nutritive sweetener are considered. Thus any presently detectable increase in bladder cancer based on past saccharin use should be viewed with considerable alarm because it could be a gross underestimation.

VIII. THE CLASSIFICATION OF SACCHARIN AND ITS REGULATORY STATUS ARE UNACCEPTABLE

This minority report already has rejected the classification of risks into categories. A policy decision which requires only labeling, logos and/or brochures for saccharin is too weak. Although the committee feels that a total, immediate ban on saccharin would be undesirable, the health hazards posed by saccharin indicate that stronger measures be taken to protect the public. Both existing and new food additives should be expected to meet the same criteria. If not already on the market, saccharin would not be allowed as a food additive and therefore should be removed. However, the institutionalization of this and other already existing products suggests that a phase-out period be recommended in such cases. A fully advertised time limit, together with vigorous education of the rationale for the eventual ban will prepare the consuming public and the manufacturers. A period of three years for the phase-out is recommended.

Concurring Views

Beverly Winikoff agrees with points I-IV, and VII and VIII, of this statement.

Charles C. Brown agrees with points I-IV, and VIII of this statement. (See his letter of February 5, 1979)

February 5, 1979

Dr. Knut Ringen
National Academy of Sciences
2101 Constitution Avenue, NW
Washington, D.C. 20418

Dear Knut:

Herewith are my views on Part 2 of the Report of the Committee for a Study on Saccharin and Food Safety Policy. Many of my views are expressed in the Minority Statement dated January 31, 1979. My thoughts on both the Report and the Minority Statement are as follows:

I agree that direct food additives should be regulated in a different manner than indirect additives. I feel that the regulatory options are simpler for these substances - a naturally occurring substance such as aflatoxin should involve some decision-making by the Department of Agriculture, whereas a direct food additive such as saccharin is solely the jurisdiction of the FDA.

I agree that irreversible health effects should be treated differently than reversible effects (note the National Research Council's Report, Drinking Water and Health, in which the different types of effects are discussed and it is stated, top of page 26, that "...different ways of arriving at standards can be proposed for each").

I agree with the statement in Item VIII under Alternative Recommendations for Saccharin in the Minority Report, "Both existing and new food additives should be expected to meet the same criteria." I believe this is the key point to be made in the saccharin issue. Uniformity of regulatory treatment is an important consideration when the chemicals in question are of the same class, i.e., direct food additives that may produce irreversible health effects (note that I make no distinction based on arbitrary considerations such as GRAS vs. nonGRAS, additive to beef vs. additive to chicken, prior sanction vs. nonprior sanction, or new vs. existing additive).

I agree that substances should be considered for regulatory action based upon their usage. Therefore, a substance can be treated as a high risk chemical in one usage category and a low risk chemical in another usage category. It also allows for different regulatory decisions to be made when the substance is a direct component of food, i.e., added in the processing, as opposed to the consumer adding it himself. This would allow for a rational decision, or series of decisions, to be made for saccharin. My own opinion on what to do with saccharin is:

(1) as an additive to drugs and dentifrices, it is of probable low risk and thus can be retained with a mild warning label

(2) as an additive included at the processing level, e.g., in soft drinks, it is of possible high risk and I would be on the side of a ban

(3) as a table-top additive, it is of possible high risk and at the very least I would recommend a very distinctive warning label especially noting pregnant women.

These actions would allow some freedom of choice though we can never hope for the public to make an "informed decision" on the basis of labels or logos.

I agree that food items should be "safer" than other environmental exposures e.g., occupational.

I agree that the Delaney clause approach is currently a reasonable methodology for food safety policy considering the present lack of knowledge concerning the quantification of health risks and benefits of all types—health, economic, or perceived benefits.

I disagree with the three risk category approach. I think it simply sidesteps the current issue of a Delaney ban, yes vs. no, and substitutes two issues (1) which risk category (how does one define risk, on an individual basis, on a potency basis, on a population basis), and (2) after the risk category is determined, the issue of what to do about it (ban, warning labels, etc.) must be resolved. I believe that the FDA should attempt to rank all existing food substances (by class) in some priority order of importance based upon the potential risk to an individual (depending upon existing data), the populations exposed and their levels of exposure, and the severity of the potential health hazards. These should then be considered in priority order and decisions made to either regulate the substance or obtain additional information.

In summary, I believe that this report should begin by stating that the Committee believes this to be the first step in a potentially long, necessarily involved, study of the food safety policy question and that Congress should not act in haste. This report should note the considerable disagreement among committee members concerning both the scientific and policy issues discussed. It should also be noted that the scientific issues are of such a basic nature that the scientific questions will not probably be solved in the near future and thus any food safety policy must be cognizant of this basic fact.

With regard to the individual issues raised in the minority report,

I agree with general items I-IV;

I would not include general items V and VI since they both pertain to this report as a specific recommendation for a food safety policy. I do not believe it to be such but rather a philosophy upon which to base such a policy, albeit a philosophy with many holes;

I disagree with recommendation VII on Saccharin - I believe that we should wait for a confirmation of the one positive epidemiologic study (one such positive study should not be a trigger for necessary action in the face of all the negative studies - even though I personally believe the positive Canadian study to be valid, I can see no reason not to postpone the regulatory decision for upwards of one year). Let me also state that I do not believe that epidemiologic confirmation of positive animal studies is necessary for FDA regulatory decisions, but I consider the saccharin issue to be of special political importance and I would wait a short period of time in order to base any decision on all the potentially important relevant information.

I agree with recommendation VIII on saccharin - if a decision was to be made today, I would consider each usage separately and not consider saccharin as a single food additive entity.

I hope this gets to you in enough time to be of some use.

Sincerely,

CHARLES C. BROWN (Sign.)

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SUPPLEMENTARY COMMENTS

Several persons expressed opinions on specific parts of this report, or wished to record thoughts on food safety that they felt were not covered in sufficient detail in the body of the report. These persons do agree with the content and major recommendations of the report. Comments were received from the following persons: Richard L. Hall (Committee), Eliot Stellar (Panel I), Robert W. Miller and Beverly Winikoff (Panel II), Marshall Shapo (Panel II), and Stephen G. Breyer and Thomas Ehrlich (Committee).

SC-2

McCORMICK & COMPANY, INC
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HUNT VALLEY, MARYLAND 21031, U S A

RICHARD L. HALL
VICE PRESIDENT
SCIENCE AND TECHNOLOGY

January 29 1979
(slightly revised 2/23/79)

Frederick C. Robbins, M.D.
Dean, School of Medicine
Case Western Reserve University
2119 Abington Road
Cleveland, Ohio 44106

Dear Fred:

I am sorry I could not be present for the last hour of the January 22 meeting. I think you and our colleagues are entitled to know my own views on saccharin, and the rationale behind them, and I would welcome similar expressions from others.

I concur in the general tenor of the conclusions expressed in the January 15 draft. I also concur in the scientific findings in Part 1 of the report, with some qualifying, though not negating, comments noted below.

1. We must regard saccharin (S) as a carcinogen in rats under the conditions of the three bigenerational studies, and therefore as a potential carcinogen in humans.

2. We cannot estimate confidently (underscoring mine) the potency of S as a possible cause of cancer in humans, but the imperatives of public policy compel us to arrive at some revisable estimate of the most probable size of the risk.

3. Current epidemiological data permit an estimate of from zero to 1,000 deaths in the U. S. from bladder cancer possibly attributable to S. Studies now under way may alter this estimate--or may not.

4. Current data persuade me that the most probable risk is much nearer zero than 1,000 (i.e., much toward the low end of the "moderate risk" category). Among these are:

    a. Saccharin does not bind to DNA.

    b. The evidence that it is not metabolized is persuasive.

    c. Both animal and epidemiological data are more consistent with (1) the action of a substance that produces effects at high level overload different from those produced at low levels, than with (2) the action of the typical chemical carcinogen which binds (or whose metabolites bind) to macromolecules by presumably the same mechanism(s) at all levels of exposure.

5. One must weigh, more earnestly and deeply than Panel I was able to do, the uncertain, unproved but possible health benefits of S, or put conversely, the risks of not having a non-nutritive sweetener (NNS). The data on benefits are poor, and the available studies are conflicting, inadequate, and insensitive. But if only a small percentage of current S users are using it effectively in weight control, these benefits could well outweigh a small and uncertain bladder cancer risk. We have no proof, but common sense and much testimonial and anecdotal support suggest that at least some people use it effectively.

6. I feel we must question the MRCA-based data on S consumption, especially by the young, without as yet accepting any other figures as clearly better.

7. Thus I believe current information suggests that the net benefit of S is small, uncertain, but probably positive. This is precisely the situation in which informed individual choice should have free scope, and where the consideration of other benefits--psychological, aesthetic, and economic--is appropriate.

But we need not accept this situation as unimprovable. We can perhaps reduce the cancer risk by better labeling and some modest restraints on distribution (see Options E and F, Appendix G; Options 5 and 6, Chapter 10) without interfering significantly with possible benefits. We can force technology and, even more productively, force regulation by recommending that food additive uses of S (i.e., incorporation into prepared foods) be discontinued after perhaps three or four years. This should be subject to change in the light of new, properly reviewed, epidemiological or experimental data. Such a phase-out should be accompanied by a clear signal to industry and the FDA to support expeditious review and, where possible, clearance of other NNS's during that time. Here is a good example of where diversity could substantially reduce apparent risk.

8. There will be those whose strong views on the risk from sweeteners in the diet cause them to oppose any measures to cater to our sweet tooth. That issue should be resolved separately by more data and education, not by the indirect means of excluding even NNS's from the diet for alleged other reasons. Imposed asceticism--particularly deviously imposed asceticism--is inappropriate in a free society.

With best personal regards.

Sincerely,

Dick

R. L. Hall

RLH:JLK

Copies: Dr. Elena O. Nightingale✓
Professor Don K. Price
Committee for a Study on
Saccharin and Food
Safety Policy

SC-5

Recommendation on Saccharin

Eliot Stellar

January 23, 1979

In my estimation, saccharin is a substance of moderate risk. This view derives from my view of the scientific evidence at hand as a member of Panel I and the discussion we had in the joint meeting of Panels I & II on January 22, 1979. In brief, saccharin is assessed as a weak carcinogen. It is perceived to have potential benefits to those who must reduce caloric intake (the diabetic and the obese) and in the reduction of dental cavies by many consumers, patients, physicians, and dentists. Therefore, the consumer should have the opportunity to make an informed choice about whether or not to ingest saccharin in his diet.

If Congress follows our general recommendation about food safety and delegates appropriate authority to the FDA, then saccharin will fall into the category we have called moderate risk and it will be available to the consumer with suitable warnings and restrictions. Every reasonable means should be taken to control saccharin ingestion, including effective education of the public on both its dangers and the question of its benefits, warning labels and descriptive circulars, restricting its availability to children and pregnant women, and perhaps most important, reduction of the concentration of saccharin in soft drinks and other foods to the lowest levels consonant with satisfactory sweet taste.

Every reasonable step should be taken to find a suitable substitute for saccharin through new research initiatives. Ideally this would be a non-caloric or non-nutritive sweetener without toxicity that is chemically stable and also inexpensive. At present, there is no known substitute for saccharin that even approaches these requirements.

Further research on the risks and benefits of saccharin should also be pursued. Of special interest are the human epidemiological studies of saccharin's carcinogenicity now underway. If they offer direct evidence of a cancer risk to humans, then saccharin use sould be phased out over a period of a few years and the warnings and restrictions stepped up. If on the other hand, these studies fail to provide direct evidence for saccharin's carcinogenicity in humans, then further studies should be undertaken, investigating saccharin's effects in people ingesting saccharin in the highest quantities for the longest periods of time.

At this point, the FDA would be in the position of continually monitoring the risks and benefits of saccharin. Then, given our present recommendations, it would be able to use its discretionary authority to tighten or loosen the control of saccharin use, depending upon its assessment of the scientific findings, its evaluation of the success of similar regulation in other industrialized countries.

SC-7

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE

TO : IOM, Panel II, Food Safety Committee

DATE: February 2, 1979

FROM : Robert W. Miller, M.D. and Beverly Winikoff, M.D., MPH

SUBJECT: Some thought on priorities concerning food safety

At a meeting of the Subpanel on Health Effects, a potentially useful perspective of priorities with regard to food safety regulation was developed. The perspective appears in the report, but we feel it is not sufficiently elaborated there. Here, for the record, is the essence of the Subpanel's discussion on this matter.

As noted in Chapter 1, food safety with respect to chemicals may be affected not only by additives, but also by contaminants and natural constituents of the diet, such as fats, salt and sugar. Considerable evidence exists for adverse health effects from excessive use of certain dietary components; e.g., salt, which contributes to hypertension, or certain fats which contribute to cardiovascular disease and probably specific cancers. Chemical contaminants in food have caused severe brain damage due to methylmercury. PCBs have caused infants to be born small for date, and have caused chloracne in children and adults. In contrast, the evidence for food additives as a cause of human disease is as yet inconclusive. Thus we come to the following rank order:

Present concern of regulators	Knowledge of adverse health effects
1. Additives	1. Natural dietary constituents
2. Contaminants	2. Contaminants
3. Natural dietary constitutents	3. Additives

First, the greatest reduction in disease would come from modificaton of the overall diet pattern. Many strategies for producing such change have been discussed in other political and scientific forums. Second, the problem of chemical contamination is growing immensely, as illustrated by the Love Canal and buried chemicals throughout the nation, as well as by PBB contamination through the entire lower peninsula of Michigan. Fish have been poisoned with kepone in Virginia, with PCBs in the Great Lakes, and with methylmercury in various waterways. Regulations can diminish exposure to food contaminants in the future and thus reduce the potential for disease substantially.

Third, Panel I has concluded that saccharin is a carcinogen, and the same may be true of other additives not yet fully evaluated. Regulation of these chemicals represents prophylaxis against the possibility that disease might be induced when many millions of people are exposed to low doses of certain food additives.

The discrepancy in the priorities noted above deserves further thought.

SEPARATE REMARKS OF MARSHALL S. SHAPO ACCOMPANYING THE REPORT FOOD SAFETY POLICY: SCIENTIFIC AND SOCIETAL CONSIDERATIONS

A document this long, dealing with a matter of this complexity, poses special problems for members of a panel asked to subscribe their names to it. The analogy to the writing of concurring and dissenting opinions in judicial cases is only a pallid one. Our compressed time frame exacerbates the difficulties for a process involving persons from so many different specialized backgrounds in science, law and public policy.

I propose simply to touch a number of main points on which I feel I should express disagreement, qualification or, occasionally, special emphasis with respect to assertions or recommendations made in the draft report.

First, I would like to emphasize the general premises with which I approach the subject. I begin with the principle that consumers should be allowed to choose those products they want at the prices the market dictates, absent government intervention unless there is a significant reason for the government to impinge on their choice. Proceeding next to the idea that the guarantee of a plentiful food supply is a clear primary concern of the nation, I note the obvious point that this study focuses on food safety. That focus leads me to emphasize my own notion that food safety policy should be relatively risk-averse, particularly as to situations involving long-term uncertainty. Allied to this is my premise that legislation should place particular emphasis on achieving fairness for those who may be disproportionately afflicted by disease or injury caused by consumer products. In this regard, I believe that food safety policy should give special consideration to vulnerable populations--those whose levels of information, intelligence, or sophistication is relatively low.

With these general ideas in mind, I comment on several issues to which the Committee has addressed itself:

Unified Statute. I agree that existing legislation should be revised and unified and that it should provide, insofar as possible, a single standard for food safety. However, I would emphasize that this standard necessarily will be a complex one.

Risk. I wish to stress my unqualified support for the language in the report that emphasizes that problems of food safety policy are problems that center on risk. Certainly, in some cases decision makers will have to take account of benefits. The centrality of the problem of risk and the friction created by the benefits issue present tensions that may not fully be resolvable by legislative language, and indeed parts of the report seem to reflect the tension that the Committee and Panel felt on this subject.

Unavoidably, Congress must face the questions of how much risk Americans are willing to buy and of how much risk Congress will let them accept. My instinct is to be quite conservative with respect to uncertain long-term risks. Various recent episodes in which growing suspicion surrounds particular products of our recent chemical revolution confirm me in this view. My position on this matter is also colored by the relative general abundance that consumers in this society are privileged to have. Obviously, I would discount my risk-aversion to long-term uncertainties if it could be shown that a particular product generated concrete goods, otherwise unattainable, particularly for disadvantaged members of the population. It can be argued that this is the case, in different ways, with the case of nitrites and with the case of saccharin. I do not think, however, that we can wave the wand of "consumer choice" and believe that we have fully discharged the obligation of government--which when it makes decisions not to regulate risks which it knows or suspects to exist effectively may be making decisions on behalf of consumers to accept those risks.

Having articulated this risk-averse perspective, and agreeing that any system of food safety policy must discriminate in some way among risk levels, I am not opposed in principle to the tripartite classification system to which the report refers. I am skeptical about its usefulness, however, because of what I suspect will be the tendency of concrete situations to outrun such classification schemes, as well as the difficulty of attaching particular administrative responses irredeemably to specific categories. I do think that any legislative reform will have to give considerable discretion to administrators to select combinations or mixtures of remedial strategies that are appropriate to the peculiar clusters of risk associated with each controversial product.

I am in accord with the proposition that similar risks should be treated similarly, however they are created. I should note, however, that because of the varied circumstances surrounding particular products, including their historical backgrounds, the search for equity across the spectrum of food products will often yield less than satisfactory answers. Indeed, it may be added in this connection that the effort to equalize responses to risk across product and activity frontiers--e.g., as between food regulation and drug regulation, or between either of these areas and occupational safety and health--is likely to yield a very jagged line of risk, or risk-benefit combinations.

Benefits. The benefits problem is surely a complicated one, involving considerations of politics and taste that are not easily cabined in statutory language. I do question seriously whether the qualities of "good taste, esthetic appearance, convenience, [and] familarity" are appropriately considered under the heading of "health" benefits. I do not deny that each of these factors has utility to consumers provable by marketplace purchases, but I think it is stretching language to call them "health benefits."

Concerning a rather different issue related to benefits, I am sensitive to the problem of what might be called the case of "unique" benefits. For a product that conferred advantages on consumers not duplicable by any other product, I would clearly be prepared to give regulators considerable leeway to permit relatively high risks. But I believe that one must always ask how "unique" the benefit truly is in such cases. Further with reference to this kind of case, I must express my skepticism of the notion that there exist significant incentives to develop substitutes for risky products so long as they are, in effect, freely marketed.

Some issues cut across categories of risk and benefit. Such a problem, complicating efforts aimed at the laudable goal of judging similar risks similarly, is inherent in the existence of established consumer preferences, at least in cases in which those preferences indicate consumer willingness to accept risks. Recognition of this acceptance may be the only way to rationalize the vexing problem of cigarettes, which, to borrow a phrase, has appeared as an embolus in the channels of our deliberations. Saccharin puts the special problem of a case involving established preferences, but one in which we do not have so clear-cut an indication of consumers' willingness to accept risks in which they have been well educated.

Decision Techniques. The "decision tree" featured in chapter four represents an interesting and creative attempt to rationalize the process of government involvement in food safety policy. So long as it is understood to be an illustration of decision-making processes, and not a definitive recommendation, I applaud it. I do express my concern that this kind of scheme may not so fully allow the overall consideration of problems that is possible with an approach that weighs groups of factors against each other. The decision tree does facilitate a focus on considerations seriatim, but it may not work so well in dealing with tight clusters of multiple competing considerations that influence close cases. In this regard, I am simply suggesting that there may be a trade-off between the kind of precision that is achievable with the decision tree and the judicious overall view of a problem permitted by the technique of lining up several factors on both sides in cases where the considerations appear to be almost in balance.

Information Strategies. I must record my dubiousness about the optimism implicit in the draft report concerning the use of information strategies. I maintain a strong belief that the market presents the happiest solution to problems of resolving differing individual preferences. The necessary qualification is, "when the market works," and it is this qualifier that contributes to my ambivalence. In this connection I note my skepticism that an appropriate amount of government resources would in fact be devoted to publicizing potential risks under an information-strategy regime, defining appropriate in this sense to mean sufficient information to promote or permit reasoned choice. I refer, only illustratively, to the statement in the draft at 9-10 that "the Committee believes that a strengthened information program that uses easily identified logos as one of several methods of communication can be effective in enabling informed consumer choice." I do not wish to load too much anxiety upon a single sentence. Yet this declaration seems symptomatic of a rather facile assumption that an information strategy would be implemented with an adequate commitment of resources.

Similarly, the proposals for logos, which to an academic eye can certainly be viewed as respectable model building, seem to me rather dubious when one considers the likely practical outcome. Moreover, I would predict that administrative decisions on logos would foment a significant amount of costly litigation. And I think it questionable whether the interest of vulnerable[1] consumers would be represented in this litigation with the same devotion and financial support as that of the producer community.

With regard to pursuit of an information-centered approach, one particular point deserves mention with respect to existing regulatory potential. Since Section 5 of the Federal Trade Commission Act gives the Commission broad powers to prohibit deception or unfair practices in commerce (additionally, Section 12 of that Act specifically declares unlawful false advertising for food) the Commission's historic role in the regulation of advertising might be considerably enhanced with reference to the food safety problem. I am not suggesting that a new statutory scheme should encourage an expanded FTC role. Indeed, it might be better if a statutory revision articulately emphasized the power to regulate advertising of a reconstituted food safety agency. I am only raising the issue of whether Congress might wish explicitly to create new authority or to emphasize existing governmental power to regulate deception in food marketing.

A further concern, which serves to bridge my discussion of information strategies to my references below to considerations of fairness, has to do with the multiplicity of risks that confront consumers. Congress must consider not only the number of hazardous substances in the marketplace but also the number of sources which may provide exposure to the same risky product. This is a problem both from the standpoint of conveying information in a context of limited communication channels and from the point of view of the limited receiving capacity of consumer minds besieged by dozens of product messages each day.

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[1] In using the term "vulnerable consumer," I am not suggesting that all consumers are "vulnerable" on all issues but only that there are groups which are vulnerable on certain issues that would be disadvantaged by theoretical reliance on an information strategy.

Fairness. Disadvantaged populations often must call on legislation for relief from injury-threatening conditions or events. The problem of fairness in the food safety arena is an exceedingly difficult one. Besides making general reference to that problem, I want to emphasize the particular plight of the special population that is likely to consume a substance which it vaguely knows carries risks in a setting in which most of the social factors operate to encourage consumption. I also wish to note the mixed issues of efficiency and fairness that surround susceptible groups who may not know of their susceptibility or whose exposure to foods dangerous to them, and promotion campaigns for those foods, may actually tend to undercut the freedom of choice that a market model requires.

Causation. One of the most difficult problems in the formulation of a rational food safety policy is that of determining what "the facts" are about causation, especially since the "facts" are truly artifacts of scientific investigation. With appropriate reserve, scientists studying these issues often say that although they believe they have solved a problem satisfactorily, there remains much room for investigation and much latitude for public policy dispute. A revised statutory framework must leave substantial flexibility for regulatory response to new discoveries about causation. It should also facilitate the preservation of a skeptical attitude toward apparently definitive findings of safety.

Further with reference to the causation issue, a particular suggestion is in order about draftsmanship. Congress should be careful in any legislative revision to spell out, either in the statutory text or in legislative history, what it means by "causation," "cause," "induce" or any other words that may be used to indicate a cause-and-effect linkage between the ingestion of food products and the development of disease. The problem of saccharin as a "promoter" emphasizes the need to make legislative intent clear on this point.

The Delaney clauses. The controversial Delaney clause merits specific comment. I wish to record my view that this provision--which has been passed three separate times by different Congresses--represents, on balance, wise public policy. I do not deny the force of the contrary arguments, and I do not think the issue free from doubt. But it does seem to me that this Report itself is instinct with the notion that cancer is, in fact, different, and that the public's concern about that group of diseases represents a rational response to a subject with obviously emotional overtones. It may well be that general safety provisions would produce the same results as the Delaney clauses in practically every case. Yet, I believe that the determined opposition to this legislation is a telling phenomenon. Using language drawn from the scientific side of the Delaney debate, I believe that this outcry represents a considered judgment that at least as a legislative "promoter" if not as an "initiator," the clause will affect results and that it is valuable for what might be called its watchdog function. Placing the problem in the decision tree in chapter 4, I would be inclined to say at point "L" that, conceding the general rationality of an analysis incorporating benefits, the health benefits of carcinogens will so seldom justify acceptance of risks that it is appropriate to have a prohibitory rule of thumb. Part of the art of regulating activities that potentially jeopardize consumers is knowing where to stop in the acquisition of the information. A rough analogy appears in Section 16 of the Securities Exchange Act, which lays down a rough and ready percentage rule for the definition of "insiders." It is the general instinct of professionals to analyze and to keep on analyzing, to refine decisions further and further. Sometimes, however, there are economies in ending the analysis and providing a clear signal to potential actors.

Rushed judgment and future study. In closing I wish to state two concerns--one about the time frame of this study, and the other about appropriate surveillance of this problem in the future.

First I wish to reiterate my belief that there was insufficient time to conduct this study. I think that the size and quality of this report are little short of miraculous given the period during which it was, as a practical matter, produced. Yet I also believe that several months or a year's more time would have added substantial, and useful, increments of considered deliberation. Congress will undoubtedly plow much of this same ground and hold its own lengthy hearings on the subject, yet I cannot escape the feeling that the deadline for this Report--which the Committee and Panel II were told informally there was no use even to try to change--was not conducive to the kind of collegial judgment that I trust Congress would have preferred from the these bodies. This is in no way to imply criticism of my colleagues in this enterprise who have given so much time and devotion to the consideration of these difficult issues, but only to suggest that nine or ten months is not enough to comprehend a problem of this magnitude, let alone to advance even tentative solutions.

This complaint leads me to a proposal for the future: Should Congress opt for a comprehensive new piece of food safety legislation, I hope it will provide for a permanent, independent body that will review these problems in broad perspective. This recommendation emphasizes my belief in the worth of this enterprise as well as, implicitly, my criticism of the deadline that was imposed upon it.

SC-18

HARVARD LAW SCHOOL
CAMBRIDGE MASSACHUSETTS 02138

February 2, 1979

Dr. Elena O. Nightingale
NAS/Institute of Medicine
2600 Virginia Avenue, NW
Suite 600
Washington, D.C. 20418

Dear Dr. Nightingale:

Tom Ehrlich and I would appreciate your circulating this letter and our letter of November 22, 1978 to Dr. Hamburg as a separate statement to the saccharin report.

Panel II has been unable to gather the additional information described in our letter to Dr. Hamburg. Partly, this reflects time pressure. Partly, it reflects the unavailability of evidence we believe is relevant. To some extent, in our view, it also reflects a problem endemic to food regulation when scientific matters are at issue, namely, relevant evidence may exist only in a highly impressionistic or anecdotal form. Scientists are uncomfortable dealing with such evidence, though lawyers are not. Our objective in circulating our letter is to suggest that the FDA or Congress attempt to answer the questions it contains--even though doing so requires evaluating impressions and opinions--before deciding whether it is wise to restrict access to saccharin.

Yours sincerely,

Stephen G. Breyer
Professor of Law

P.S. I have just received a copy of the Executive Summary which states saccharin as belonging either to the moderate or high risk category. In my view, after having attended committee meetings faithfully, read the evidence presented, listened to the deliberations of Panel I and read its report, I find it inconceivable for saccharin to be viewed as a high risk substance. I do not believe the body of the report supports the conclusion contained in the summary.

NOTE: Thomas Ehrlich, Head of Legal Services Corporation, Washington, D.C., and a member of the Committee for a Study on Saccharin and Food Safety Policy, concurs with Stephen G. Breyer's letter of February 22, 1979, with attachments.

SC-19

HARVARD LAW SCHOOL
CAMBRIDGE · MASSACHUSETTS · 02138

November 22, 1978

Dr. David A. Hamburg
National Institute of Medicine
2101 Constitution Ave.
Washington, D.C. 20418

Dear Dr. Hamburg:

As members of the National Academy of Sciences Saccharin Study Coordinating Committee we should like to make several comments about Panel I's report -- comments which we hope will guide Panel II's efforts to reach a conclusion about a sensible regulatory policy for saccharin. In our view the Panel I Report, which collects and analyzes the well-controlled scientific studies on the subject, suggests two basic conclusions: First, a saccharin user runs an extremely small risk of cancer. A "risk of a risk" might be a better way to put it, for the scientific tests show positive cancer results in high-dose, two-generation rat studies, but there is no clear way to extrapolate from rats to humans. Second, while the use of saccharin may itself save lives (through weight control and use by diabetics) there are no well-controlled scientific studies that demonstrate this to be the case. In our view, this report does not support a ban on saccharin (contrary to some press accounts, see e.g., N.Y. Times, Sunday, Nov. 12, 1978) but rather it poses a basic problem: How is one to make a wise regulatory decision in the face of such scientific uncertainty?

We believe that Congress was right in suggesting that this decision be based upon an effort to weigh health risks against health benefits. This weighing need not involve the troubling trade off between "lives and dollars" or "lives and psychological benefits." But, rather it means here that any final decision about saccharin should meet the following basic test: "The decision, when implemented, must, on balance, save lives." That is to say, a decision which in fact causes more deaths than the contrary decision would be wrong. Moreover, in applying this test, one should go beyond the limited amount of rigorous, scientific tested evidence that now exists. The absence of well controlled scientific studies demonstrating health benefits and of scientific methods for extrapolating from rats to humans does not mean: 1) that there are no benefits, nor 2) that there are no risks, nor 3) that the existence of some risks means "ban." Rather, it means that a decision maker should turn, in part, to other, more impressionistic evidence, such as well informed opinions of medical practitioners in the field to obtain subjective assessments of the degree of risk and benefit. While the notion of relying on more subjective assessment makes scientists uncomfortable, it is familiar to lawyers and others who work in areas where the absence of well controlled scientific studies is the rule.

We believe that Panel I might provide some additional help in deciding whether a total or a partial ban on saccharin would cause more deaths than it would prevent. To be more specific:

1. How likely is it that a partial or total ban on saccharin will itself cause injury to health or death? The Panel analyzes this question in respect to weight gain, diabetes, tooth decay, and medicines. Yet, might it not have gone further in respect to one crucial potential health benefit: the prevention of overweight? This issue breaks down into three subsidiary questions:

a. To what extent is being overweight itself a cause of death because of increased risk of heart attacks, strokes, or other diseases? This is a scientific question on which, we suspect, there is more specific evidence than the Report contains. Is it not possible to describe how much weight how many persons would have to gain before we run risks roughly comparable to the risk of cancer deaths (on various assumptions about that risk)?

b. If saccharin users substitute sugar for saccharin, to what extent are they likely to gain weight? This question is obviously difficult to answer, for as the Panel points out, no one knows, for certain whether a person who eats more sugar will, at the same time, cut down on other calories. Still, is this not an area where doctors' impressions would prove useful? And, could the panel not help to evaluate such subjective evidence?

c. To what extent will restrictions on the availability of saccharin lead its users to susbtitute sugar? This question probably cannot be answered scientifically because the answer obviously depends upon what restrictions are placed on the use of saccharin and because there is little evidence about how people will act when deprived of diet drinks: will they switch to iced tea or to Coca Cola? Despite the lack of evidence, a rational decision-maker (not necessarily the Academy or the Panel) must make a working assumption -- even if based only on rough impressions -- if he is to avoid violating the fundamental 'life saving' criterion.

2. Is it not possible to obtain a somewhat more precise idea of the scope of the risk?

a. Would it help to ask practitioners in the field about bladder cancer? Would their noticing, or failing to notice, use of saccharin by their patients, help put a ceiling -- even a subjective one -- on the number of likely saccharin induced deaths?

b. Would it help to trace saccharin use and bladder cancer rates further back in time? Because of the potentially long lag, should "use" data before 1950 be examined? If no correlation between increased saccharin use and bladder cancer deaths then can be found, does that fact suggest a ceiling on probably saccharin induced deaths? In this regard, what is the signficance of increased use of saccharin by children? The bladder cancer data suggests that it is a disease of old age, with very little incidence before ages 55 or 60. Are lags usually that long?

3. Is it possible to use the data to help to evaluate more precisely particular policy options? For example, the data on animal studies seems to show risks to male, not female, animals. Moreover, the animals at risk were those exposed during their entire lifetimes including in utero. Further, the Report suggests that a human being will eliminate all saccharin as waste if he abstains for two or three days. Do these facts suggest that most or all of the risk could be eliminated if saccharin was not used by males only; or was

not used by pregnant women only; or if those using it abstained for two or three days a month? Should appropriate labeling suggest these possibilities?

We raise these questions because we believe doctors and scientists, such as those on the NAS panel and others providing information to it, may find it easier to answer them (despite their subjective and judgmental nature) than Congress or regulators. Moreover, the matter is important. Our reading of the papers sent and what we we have heard at meetings leads us to believe that saccharin causes very few deaths. Indeed, were we forced now to guess at a number, it would be under 200 or so per year. On the other hand, we have the impression that eating sugar is associated with a large number of diseases, through leading to excess weight and otherwise. Moreover, our own personal judgment is that, if saccharin is restricted, many persons will indeed use more sugar. And those who will find it most difficult to obtain saccharin as a prescription or even as an over-the-counter drug are those persons who do not habitually use drugstores, who are located far from them, who are immobile, or who are badly educated. Since many such persons may consume diet drinks each day, we see a risk that restrictive regulation might save a handful of persons from bladder cancer while leading more to die prematurely of strokes or heat disease. This matter should be explored more thoroughly.

For these reasons we hope that Panel I will continue to provide views and information as Panel II tries to answer the relevant policy questions.

Yours faithfully,

Stephen Breyer

Tom Ehrlich
Thomas Ehrlich by SGB

APPENDIXES

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APPENDIX A

Public Law 95-203
95th Congress

An Act

To require studies concerning carcinogenic and other toxic substances in food, the regulation of such food, the impurities in and toxicity of saccharin, and the health benefits, if any, resulting from the use of nonnutritive sweeteners; to prohibit for 18 months the Secretary of Health, Education, and Welfare from taking certain action restricting the continued use of saccharin as a food, drug, and cosmetic; to require certain labels and notices for foods containing saccharin; and for other purposes.

Nov. 23, 1977
[S. 1750]

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

Saccharin Study and Labeling Act.
21 USC 301 note.

Section 1. This Act may be cited as the "Saccharin Study and Labeling Act".

Study.
21 USC 343 note.

Sec. 2. (a)(1) The Secretary of Health, Education, and Welfare (hereinafter in this Act referred to as the "Secretary") shall arrange, in accordance with subsection (b), for the conduct of a study, based on available information, of—

(A) current technical capabilities to predict the direct or secondary carcinogenicity or other toxicity in humans of substances which are added to, become a part of, or naturally occur in, food and which have been found to cause cancer in animals;

(B) the direct and indirect health benefits and risks to individuals from foods which contain carcinogenic or other toxic substances;

(C) the existing means of evaluating the risks to health from the carcinogenicity or other toxicity of such substances, the existing means of evaluating the health benefits of foods containing such substances, and the existing statutory authority for, and appropriateness of, weighing such risks against such benefits;

(D) instances in which requirements to restrict or prohibit the use of such substances do not accord with the relationship between such risks and benefits; and

(E) the relationship between existing Federal food regulatory policy and existing Federal regulatory policy applicable to carcinogenic and other toxic substances used as other than foods.

(2) The Secretary shall arrange, in accordance with subsection (b), for the conduct of a study to determine, to the extent feasible—

(A) the chemical identity of any impurities contained in commercially used saccharin,

(B) the toxicity or potential toxicity of any such impurities, including their carcinogenicity or potential carcinogenicity in humans, and

(C) the health benefits, if any, to humans resulting from the use of nonnutritive sweeteners in general and saccharin in particular.

National Academy of Sciences, conduct of studies.

(b)(1) The Secretary shall first request the National Academy of Sciences (hereinafter in this section referred to as the "Academy"), acting through appropriate units, to conduct the studies, required by subsection (a), under an arrangement whereby the actual expenses incurred by the Academy directly related to the conduct of such studies will be paid by the Secretary. If the Academy agrees to such request, the Secretary shall enter into such an agreement with the Academy.

Agreement.

(2) If the Academy declines the Secretary's request to conduct any such study under such an arrangement, then the Secretary shall enter into a similar arrangement with another appropriate public or nonprofit private entity to conduct such study.

(3) Any arrangement entered into under paragraph (1) or (2) of this subsection for the conduct of a study shall require that such study be completed and reports thereon be submitted within such period as the Secretary may require to meet the requirements of subsection (c).

Reports to congressional committees.

(c) (1) Within 12 months of the date of the enactment of this Act the Secretary shall report to the Committee on Human Resources of the Senate and the Committee on Interstate and Foreign Commerce of the House of Representatives (A) the results of the study conducted pursuant to subsection (a) (2) (including supporting data and other materials provided by the entity which conducted the study), and (B) any action proposed to be taken on the basis of the results of the study.

(2) Within 15 months of the date of the enactment of this Act the Secretary shall report to the Committee on Human Resources of the Senate and the Committee on Interstate and Foreign Commerce of the House of Representatives (A) the results of the studies (including supporting data and other materials provided by the entity which conducted the study) conducted pursuant to subsection (a) (1), (B) the recommendations, if any, of such entity for legislative and administrative action, and (C) such recommendations for legislative action as the Secretary deems necessary.

"Saccharin."

(d) For purposes of this section and section 3, the term "saccharin" includes calcium saccharin, sodium saccharin, and ammonium saccharin.

21 USC 348 note.

SEC. 3. During the 18-month period beginning on the date of the enactment of this Act, the Secretary—

(1) may not amend or revoke the interim food additive regulation of the Food and Drug Administration of the Department of Health, Education, and Welfare applicable to saccharin and published on March 15, 1977 (section 180.37 of part 180, subchapter B, chapter 1, title 21, Code of Federal Regulations (42 Fed. Reg. 14638)), or

21 USC 301.

(2) may, except as provided in section 4 and the amendments made by such section, not take any other action under the Federal Food, Drug, and Cosmetic Act to prohibit or restrict the sale or distribution of saccharin, any food permitted by such interim food additive regulation to contain saccharin, or any drug or cosmetic containing saccharin,

solely on the basis of the carcinogenic or other toxic effect of saccharin as determined by any study made available to the Secretary before the date of the enactment of this Act which involved human studies or animal testing, or both.

Labeling.
21 USC 343.

SEC. 4. (a) (1) Section 403 of the Federal Food, Drug, and Cosmetic Act is amended by adding at the end thereof the following new paragraph:

"(o) (1) If it contains saccharin, unless, except as provided in subparagraph (2), its label and labeling bear the following statement: 'USE OF THIS PRODUCT MAY BE HAZARDOUS TO YOUR HEALTH. THIS PRODUCT CONTAINS SACCHARIN WHICH HAS BEEN DETERMINED TO CAUSE CANCER IN LABORATORY ANIMALS'. Such statement shall be located in a conspicuous place on such label and labeling as proximate as possible to the name of such food and shall appear in conspicuous and legible type in contrast by typography, layout, and color with other printed matter on such label and labeling.

Regulation.

"(2) The Secretary may by regulation review and revise or remove the requirement of subparagraph (1) if the Secretary determines such action is necessary to reflect the current state of knowledge concerning saccharin.".

Effective date.
21 USC 343 note.

(2) The amendment made by paragraph (1) shall apply only with respect to food introduced or delivered for introduction in interstate commerce on and after the 90th day after the date of the enactment of this Act.

Report to congressional committees.
21 USC 343 note.

(3) The Secretary shall report to the Committee on Human Resources of the Senate and the Committee on Interstate and Foreign Commerce of the House of Representatives any action taken under section 403(o)(2) of the Federal Food, Drug, and Cosmetic Act.

Supra.
Retail establishments, notice, display.
21 USC 343.

(b)(1) Section 403 of the Federal Food, Drug, and Cosmetic Act is amended by adding after paragraph (o) the following new paragraph:

"(p)(1) If it contains saccharin and is offered for sale, but not for immediate consumption, at a retail establishment, unless such retail establishment displays prominently, where such food is held for sale, notice (provided by the manufacturer of such food pursuant to subparagraph (2)) for consumers respecting the information required by paragraph (o) to be on food labels and labeling.

"(2) Each manufacturer of food which contains saccharin and which is offered for sale by retail establishments but not for immediate consumption shall, in accordance with regulations promulgated by the Secretary pursuant to subparagraph (4), take such action as may be necessary to provide such retail establishments with the notice required by subparagraph (1).

Notice requirement review, revision or removal.

"(3) The Secretary may by regulation review and revise or remove the requirement of subparagraph (1) if he determines such action is necessary to reflect the current state of knowledge concerning saccharin.

Hearing.

42 USC 4321 note.
5 USC 500 *et seq.*
Judicial review.

"(4) The Secretary shall by regulation prescribe the form, text, and manner of display of the notice required by subparagraph (1) and such other matters as may be required for the implementation of the requirements of that subparagraph and subparagraph (2). Regulations of the Secretary under this subparagraph shall be promulgated after an oral hearing but without regard to the National Environmental Policy Act of 1969 and chapter 5 of title 5, United States Code. In any action brought for judicial review of any such regulation, the reviewing court may not postpone the effective date of such regulation.".

Effective date.
21 USC 343 note.

(2) The amendment made by paragraph (1) shall apply with respect to food which is sold in retail establishments on or after the 90th day after the effective date of the regulations of the Secretary of Health, Education, and Welfare under paragraph (p)(4) of the Federal Food, Drug, and Cosmetic Act.

Supra.
"Saccharin."
21 USC 321.

(3) Section 201 of the Federal Food, Drug, and Cosmetic Act is amended by adding at the end thereof the following:

"(z) The term 'saccharin' includes calcium saccharin, sodium saccharin, and ammonium saccharin.".

Vending machines, health risk statement, requirements.
21 USC 343a.

(c) The Secretary may by regulation require vending machines through which food containing saccharin is sold to bear a statement of the risks to health which may be presented by the use of saccharin. A regulation under this subsection shall require such statement to be located in a conspicuous place on such vending machine and as proximate as possible to the name of each food containing saccharin which is sold through such machine. Any food containing saccharin which is sold in a vending machine which does not meet any applicable requirement promulgated under this subsection shall, for purposes of the Federal Food, Drug, and Cosmetic Act, be considered a misbranded food.

21 USC 301.

Information, availability and distribution.

(d) The Secretary shall (1) prepare information respecting the nature of the controversy surrounding the use of food containing saccharin, and (2) provide for the distribution of such information for display by retail establishments where such food is sold but not for immediate consumption. The Secretary may review and revise such information if he determines such action is necessary to reflect the current state of knowledge concerning the risks to health presented by the use of saccharin.

42 USC 289l–1 note.

SEC. 5. (a) Section 204(d) of the National Research Act (Public Law 93–348) is amended by striking out "36-month period" each place it appears and inserting in lieu thereof "42-month period".

42 USC 218 note.

(b) Section 211(b) of such Act is amended by striking out "January 1, 1978" and inserting in lieu thereof "November 1, 1978".

Approved November 23, 1977.

LEGISLATIVE HISTORY:

HOUSE REPORTS: No. 95–658 accompanying H.R. 8518 (Comm. on Interstate and Foreign Commerce) and No. 95–810 (Comm. of Conference).
SENATE REPORTS: No. 95–353 (Comm. on Human Resources) and No. 95–369 (Comm. on Commerce, Science, and Transportation).
CONGRESSIONAL RECORD, Vol. 123 (1977):
    Sept. 14, 15, considered and passed Senate.
    Oct. 17, considered and passed House, amended, in lieu of H.R. 8518.
    Nov. 3, House agreed to conference report.
    Nov. 4, Senate agreed to conference report.

A-5

federal register

FRIDAY, APRIL 15, 1977

PART III

THE NATIONAL ARCHIVES OF THE UNITED STATES • 1934 •

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

■

SACCHARIN AND ITS SALTS

Proposed Rule and Hearing

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Parts 145, 150, 172, 180, 189, 310, 430, 510, 558, and 700]

[Docket No. 77N-0088]

SACCHARIN AND ITS SALTS

Proposed Rule Making

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: The Commissioner of Food and Drugs is proposing to revoke the interim food additive regulation under which saccharin and its salts (saccharin) are currently permitted as ingredients in prepackaged foods, such as soft drinks, and as tabletop nonnutritive sweeteners. The Commissioner is also inviting comments on a proposal to accept and promptly review new drug applications for the marketing of saccharin as a single-ingredient drug, available without a physician's prescription. If approvable under the requirements of section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355), such products would be required to bear a conspicuous warning about the risk of cancer. The Commissioner is also proposing to prohibit the use of saccharin in cosmetics that are likely to be ingested, to amend the standards of identity that provide for the use of saccharin and to prohibit the use of saccharin in animal drugs and animal feed.

The Commissioner's determination that saccharin must be banned as a food additive is based on a series of scientific studies conducted in accordance with currently accepted methods for determining whether compounds can cause cancer. The most recent of these studies, conducted by Canadian scientists under the auspices of the Canadian Government, confirms what earlier American studies have suggested: that saccharin poses a significant risk of cancer for humans. Under these circumstances, conscientious concern for the public health requires that FDA prohibit the continued general use of saccharin in foods.

This conclusion is also dictated by the so-called Delaney clause of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 348(c)(3)), which prohibits the use in food of any food additive which has been shown, by ingestion or other appropriate tests, to cause cancer in laboratory animals.

The Delaney clause does not apply to human drugs, however, and it therefore does not prohibit the approval of a drug that has been shown to cause cancer in laboratory animals if the drug provides medical benefits that outweight the potential risk. For many individuals, including diabetics who must limit their intake of sugar and other carbohydrates, the availability of a nonnutritive sweetener, may serve a legitimate medical need. The Commissioner is therefore proposing to permit the submission of new drug applications for the marketing of saccharin as a single-ingredient OTC drug, which applications must be accompanied by legally sufficient evidence of the effectiveness of saccharin for its labeled indications.

DATES: Comments on this proposal may be submitted by June 14, 1977. Published elsewhere in this issue of the Federal Register is a notice of an informal hearing before the Commissioner to be held on May 18 and 19, 1977 to hear oral comments on this proposal.

ADDRESS: Written comments should be sent (preferably in quadruplicate) to the Hearing Clerk (HFC-20), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, Md. 20857.

FOR FURTHER INFORMATION CONTACT:

GENERAL: Ronald J. Wylie, Compliance Regulations Policy Staff (HFC-10), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, Md. 20857, 301-443-3480.

FOODS: John J. McAuliffe, Bureau of Foods (HFF-334), Food and Drug Administration, Department of Health, Education, and Welfare, 200 C St. SW., Washington, DC 20204, 202-472-5690.

HUMAN DRUGS: Paul Fehnel, Bureau of Drugs (HFD-30), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, Md. 20857, 301-443-3640.

COSMETICS: Heinz Eiermann, Bureau of Foods (HFF-440), Food and Drug Administration, Department of Health, Education, and Welfare, 200 C St. SW., Washington, D.C. 20204, 202-245-1530.

VETERINARY DRUGS: Edward Ballitch, Bureau of Veterinary Medicine (HFV-231), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, Md. 20857, 301-443-3336.

SUPPLEMENTARY INFORMATION:

I. Saccharin as a Food Ingredient

A. History of the Use and Safety of Saccharin

Saccharin is a nonnutritive, artificial sweetener that is approximately 350 times sweeter than sugar. Following the discovery of saccharin in 1879, commercial interest was initially shown in its possible usefulness as an antiseptic or as a preservative to inhibit fermentation in foods, but from the beginning, questions about its safety existed. In 1886, workers in Europe noted no effects in human subjects who had been given single doses of saccharin up to 5 grams. In 1888, a French scientist reported no harmful effects in diabetics who ingested 5 grams per day for 5 months. During the succeeding decade, several reports both endorsing and criticizing the use of saccharin in diabetics noted evidence in some patients of loss of appetite, nausea, and pressure in the stomach. In the meantime, attempts to use saccharin in the treatment of intestinal infections, chronic gastritis, cystitis, and numerous other diseases proved unsuccessful. By 1907, however, canners of fruits and vegetables in the United States had developed an interest in using saccharin to sweeten their products. In 1912, a Board of Scientific Advisors to the Secretary of Agriculture, appointed by President Theodore Roosevelt, concluded that 0.3 gram/day of saccharin was safe and that higher levels of intake, especially above 1 gram/day, caused disturbances of digestion.

In numerous toxicological studies in experimental animals during the period 1920 to 1950, no findings were reported that raised serious questions about the safety of saccharin as then used. In Europe, during World Wars I and II, the consumption of saccharin greatly increased, with no apparent adverse effects among consumers, though no adequate epidemiologic studies were conducted at that time.

Saccharin use today is widespread. Approximately 6 to 7.6 million pounds of saccharin were used in the United States in 1976. It is used in food and beverages, cosmetics, drugs, animal feed, and industrial processes. Food and beverage uses are by far the most extensive, accounting for over 70 percent of the saccharin used.

The soft drink industry accounts for about 74 percent of the saccharin consumed in food and beverages in the United States. Other dietary uses, which account for 14 percent of the saccharin consumed, include powdered juices and drinks, other beverages, sauces and dressings, canned fruits, dessert toppings, cookies, gums, jams, candies, ice cream, and puddings. About 12 percent of the saccharin consumed is as a sweetener in place of nutritive sweeteners (e.g., sugar) in coffee and tea and on cereal.

Although saccharin's predominant use is in foods, it is also used in drugs—both prescription and OTC—especially those intended for pediatric use and for use by diabetics. Saccharin is also found in a variety of cosmetics, including lipsticks, dentifrices, mouthwashes, aftershave lotions, moisturizing skin preparations, hair tonics, skin cleansers, bubble baths, colognes, face powders, and douches. Saccharin is also used to a limited extent in animal feed and animal drugs.

One of the first chronic toxicity studies of saccharin was reported by Fitzhugh et al. in 1951 (discussed below). The findings of that study were inconclusive and there continued to be debate among scientists about the safety of saccharin. Accordingly, in 1955 the Committee on Food Protection of the National Academy of Sciences reviewed the literature bearing on the safety of saccharin and concluded that the "maximum probable tolerance level for saccharin in the human diet is at least as great as 1.0 gram per day." The National Academy of Sciences (NAS) committee further concluded that the substitution of saccharin for the average daily consumption of sugar in the United States would amount to about 0.3 gram of saccharin, and that "the maximal amount of saccharin likely to be consumed was not hazardous."

Because of greatly increased use of saccharin and cyclamate, another nonnutritive sweetener, as well as drastic changes in the patterns of their consumption during the 1960's, in 1967 FDA requested the National Academy of Sciences again to evaluate the safety of these nonnutritive sweeteners. In response to this request, an ad hoc committee was formed under the NAS Committee on Food Protection. In 1968, the committee issued an interim report in which it concluded that the intake of 1 gram or less per day of saccharin by an adult should present no hazard. However, the committee also recognized at that time that the existing carcinogenesis studies on saccharin, judged by current standards, were inadequate, and it therefore recommended that contemporary studies be undertaken.

During the late 1960's, saccharin was being widely used competitively or in combination with cyclamates. Consequently, when the use of cyclamate was banned by FDA in 1969, it was anticipated that the daily intake of saccharin by users of nonnutritive sweeteners would increase substantially. An ad hoc subcommittee of the NAS Committee on Food Protection was once again requested by FDA to review all available toxicity data on saccharin in the light of the projected sharp increase in use.

The NAS subcommittee issued its final report in July 1970. It arrived at conclusions regarding the safety of saccharin very similar to the assessments of 1955 and 1968. The subcommittee again recommended that chronic toxicity studies, designed according to modern protocols, be completed. It further recommended that: (a) epidemiologic studies should be carried out with emphasis on the diabetic segment of the population and in relation to pregnancy; (b) comparative metabolism studies should be done in man and in animals; and (c) toxicologic interactions with other selected chemicals should be explored.

Although the then existing studies raised some questions about whether saccharin could cause cancer, no firm conclusions could be reached on the basis of those data. In 1972, because of the questions about the safety of saccharin, FDA removed saccharin from the list of substances generally recognized as safe (GRAS) and imposed limits on the use of saccharin to discourage general use by consumers and to inhibit an increase in its use by the general population. At that time, FDA also issued an interim food additive regulation to permit continued limited use of saccharin pending completion of studies to resolve the questions concerning the safety of saccharin. In issuing the interim regulation, FDA concluded that the continued limited use of saccharin did not constitute a significant risk to public health.

B. HISTORY OF SCIENTIFIC AND MEDICAL INQUIRY INTO THE CAUSES OF CANCER

Sir Percival Potts' description, almost 200 years ago, of the relationship between exposure to soot and cancer of the scrotum in chimney sweeps is usually cited as marking the beginning of studies in environmental carcinogenesis (Ref. 1). It was not until the late 19th century, however, that the association between exposure to aromatic amines and the production of bladder cancer among workers in the German dye industry was established, and only in the early part of this century that the production of skin cancer by X-radiation and radium became evident.

Modern research on chemical carcinogenesis dates from the classic studies of Yamagiwa and Ichikawa (Ref. 2). They successfully induced cancer by applying coal tar to the ears of rabbits and thereby produced the first experimental animal analogy of a type of chemically induced human cancer. The work of these Japanese investigators in 1915 was quickly followed by similar investigations in many laboratories and culminated in the isolation from coal tar of the carcinogenic polycyclic hydrocarbon benzo[a]pyrene by Kennaway and Cook (Ref. 3). But it was only in 1938 that Hueper experimentally produced bladder cancer in dogs by administration of β-naphthylamine (Ref. 4).

The known causes of human cancer include physical, chemical, and biological agents. According to Boyland (Ref. 5)

> Reasonable estimates are that not more than 5% of human cancer is due to viruses and less than 5% to radiations. Some 90% of cancer in man is therefore due to chemicals, but we do not know how much is due to endogenous carcinogens and how much to environmental factors. An expert committee (WHO, 1968) has concluded that at least half of all cancer in man is due to environmental factors. It should therefore be possible to prevent a great deal of human cancer by finding and removing chemical carcinogens from the environment.

In 1960, Dr. G. B. Mider prepared for a committee of the United States Congress a summary of the current state of scientific knowledge about the causes of cancer (Ref. 6). Despite major subsequent advances in our understanding of the role of microsomal enzyme metabolism in the action of carcinogens, in molecular biology, in virology, in our knowledge of the immunological aspects of cancer, and in the development of in vitro models for carcinogenesis, the summary of the causes of cancer prepared by Dr. Mider more than a decade ago is still essentially correct:

> (1) Although cancer can be caused by extraneous agents, not all members of the exposed population will develop cancer. Those who are most susceptible can be identified only by experience.
>
> (2) Even a powerful carcinogen requires weeks or months to elicit cancer in mice or rats and probably requires years in man.
>
> (3) No change need be recognizable in the organ or tissue destined to become cancerous before the cancer itself appears.
>
> (4) Experience in the laboratory does not predict unequivocally the reaction of humans to the same agent. On the other hand, those few chemical and physical agents known to produce cancer in man, with the possible exception of inorganic arsenical compounds, have elicited cancers in animals.
>
> (5) No one at this time can tell how much or how little of a carcinogen would be required to produce cancer in any human being, or how long it would take the cancer to develop.
>
> (6) The effect of certain chemical carcinogens can be markedly increased by other compounds with little or no carcinogenic power.
>
> (7) The accumulated evidence suggests the irreversibility of the cancerous response once it has been initiated and further suggests a cumulative effect.
>
> (8) The most potent carcinogens, by their very strength, are almost sure to be discovered clinically. It is assuredly the less potent carcinogens that seem most important in human cancer and provide the real problem for evaluation. A major objective of experimental carcinogenesis is, therefore, the bioassay for the presence of weak carcinogens.
>
> (9) Chemical configuration alone cannot be used to predict the ability of a new compound to produce cancer.
>
> (10) Possession (by a substance) of a biological effect known to be associated with a particular type of cancer production, may be of importance in assessing potential carcinogenicity. Examples are: estrogenic activity, goitrogenic activity, production of liver cirrhosis.

The special attention given to the prevention of cancer is reflected in the Food Additives Amendment of 1958 and Color Additive Amendments of 1960. In principle, both laws recognize that all substances have a potential for harm and that, conversely, there are conditions under which most substances may be used safely. However, both laws also provide that under no conditions are cancer-producing substances to be considered safe. This Congressional expression of concern about cancer-producing agents indicates the need to know about the cancer-producing potential of food additives.

USE OF ANIMAL TESTS TO IDENTIFY RISKS TO HUMAN HEALTH

Testing for acute toxic effects in animals has long been and remains today the primary basis for evaluating the safety of food for humans. Now, however, scientists also test substances in animals to assess their long-term, or chronic effects, including their potential to cause cancer.

The first chronic animal studies were conducted in the late 19th century, after it was found that certain diseases were associated with lack of certain essential dietary constituents. For example, vitamin C deficiency, which leads to scurvy and niacin deficiency, which causes pellagra, were extensively studied in animals after scientists discoverd that these diseases could be mimicked in animals. After it became apparent that laboratory animals were useful in studying nutritional diseases, scientists quickly concluded that animal experience might also be useful in predicting the long-term effects in man of ingestion of small amounts of chemicals. In the early 1930's, FDA scientists initiated some of the first long-term, or lifetime chronic feeding studies on substances to which humans are exposed. These studies—on lead arsenate pesticides—led, in 1940, to the establishment of limitations on the use of lead arsenate.

Since these early days of toxicology, the use of tests in laboratory animals to predict the long-term chronic effects of chemicals in man has been accepted by virtually all scientists and is today used by every technologically advanced country in the world. In the United States, many Federal agencies in addition to FDA, such as the Environmental Protection Agency and the National Cancer Institute, rely on these animal tests to assess the safety of a variety of compounds. In 1964, the National Academy of Sciences/National Research Council (the Academy) published a report entitled "Principles and Procedures for Evaluating the Safety of Intentional Chemical Additives in Foods." This report updated pamphlets published in 1951 and 1952 on the safe use of chemicals in foods. The 1964 report and subsequent publications by the Academy describe the widely accepted approach of animal tests for evaluating the safety of chemicals added to foods. The World Health Organization has also espoused the use of animal tests to assess the safety of food ingredients.

The difficulty of identifying chemicals that may cause cancer has been considered may times in the last 15 years, and distinguished expert committees of the World Health Organization, Food and Agricultural Organization, National Academy of Sciences/National Research Council, and Department of Health, Education, and Welfare, as well as FDA, have published reports setting down principles and guildelines. Again the accepted test model is the chronic test in laboratory animals. As Berenblum (Ref. 8) has pointed out, our existing knowledge does not provide a basis for firm agreement on the optimal conditions for carcinogenicity testing, but merely allows the setting down of minimal requirements for animal tests for carcinogenicity. These minimum accepted requirements include: (1) more than one species of animal should be used to demonstrate lack of carcinogencity; (2) continuation of testing for the "practical" lifetime of the animals to establish a negative finding; (3) use of test doses close to the pharmacologically active range, several orders of magnitude above the actual use level; (4) maximization of numbers of animals on test, recognizing the practical limitations on population size; (5) use of routes of administration analogous to those by which humans will be exposed; and (6) whenever possible, commencing exposure during pregnancy and continuing exposure in the offspring for a lifetime. The three principal tests of saccharin on which the Commissioner is basing the accompanying proposals generally meet these basic criteria.

Even with the best test system, it must be recognized that a positive result only labels a substance as a suspect human carcinogen; at the same time, a negative result does not necessarily exclude the possibility that the substance is carcinogenic for man. Furthermore, it should be remembered that absolute demonstration of noncarcinogencity, even in the species tested, is impossible. As J. Cornfield has indicated:

> Expression of results as confidence limits rather than as a test of significance is to be preferred, since even when the lower confidence limit is below zero and no positive evidence exists, the upper limit may well be above zero, and this will serve as a constant reminder that failure to uncover positive evidence of carcinogenicity is not the same as a positive demonstration of noncarcinogenicity (Ref. 9).

Questions are frequently raised about the significance of carcinogensis observed in animal experiments based on the belief that the high dosages to which animals are customarity exposed have no relevance in the assessment of human risk. Indeed, such questions have been raised about the findings in the WARF, FDA, and Canadian studies that saccharin causes bladder cancer. The Commissioner therefore believes that it is important to clarify this crucial issue.

It should be recognized that, general, only high dosages will produce tumors in animals under the experimental conditions that must customarily be employed. In setting up model experimental systems, scientists have no choice but to use relatively small numbers of animals in comparison to the human population likely to be exposed. In order to obtain meaningful, consistent, and reproducible results, studies must be designed to produce a significant number of cancers in the animals under test.

Even as low an incidence of cancer as 10 percent in a group of 100 experimental animals, which would approach the limit of reproducibility, would exceed any acceptable human risk. An incidence of 0.01 percent would represent 20,000 out of the total U.S. population of 200 million, and would certainly be considered unacceptably high. But to detect such a low incidence in experimental animals using dosage levels comparable to those administered to humans would require literally tens of thousands of animals. For this reason, scientists administer large doses to relatively small groups of experimental animals and then extrapolate the results to estimate the risk of cancer at low dosages.

Several methods for making such calculations of risk have been employed, but based on present knowledge and experience, the Commissioner believes the proper conservative approach is to assume a direct proportionality between the size of the dose and the incidence of tumors. For example, if a daily dosage of 1 gram per kilogram (kg) fed to experimental animals over a 2-year period produces a 10 percent incidence of tumors, FDA would assume that there would be a 1 percent incidence with 0.1 gram per kg dose, or a 0.1 percent incidence with a 0.01 gram per kg dose. Using this method of calculation, the agency would estimate, conservatively, that if a substance produces a 10 percent incidence of cancer in the rat at a dose of 1 gram per kg, it would produce a 0.01 percent incidence, representing 20,000 persons out of a total population of 200 million, if ingested by man at a dose of 1 milligram per kg.

It is important to recognize that such calculations may indicate only a minimal risk. Experimental assays are conducted under controlled dietary and environmental conditions with animals o homogeneous genetic background, whil humans live under diverse conditions and are genetically heterogeneous, and are therefore likely to include subpopulations of unusual susceptibility.

Another popular misconception about the use of high dosages in animal carcinogenesis testing is the belief that any substance will induce cancer in animals if fed at sufficiently high levels. Excessively high levels of most substances can induce toxic effects in animals, but only a small number of such substances can produce cancer. This fact is illustrated by a study of 120 pesticides and industrial chemicals reported by J. R. M. Innes, et al. (Ref. 10). The compounds were selected on the basis of toxicity evidence suggesting potential harm to man, widespread use, or chemical structure suggesting possible carcinogenicity. In this study, both sexes of 2 hybrid strains of mice were orally administered maximum tolerated doses of the 120 test compounds starting at the age of 7 days. The authors found that administration of only 11 of the compounds unequivocally induced a significantly elevated incidence of tumors.

B. CARCINOGENICITY TESTING OF SACCHARIN

The first long-term study to evaluate the chronic toxicity of saccharin in the diet of rats was reported at FDA in 1951 by Fitzhugh, Nelson, and Frawley (Ref. 11). Various levels of saccharin were fed, some as high as 5 percent of the diet, to 10 male and 10 female rats per dosage level. At the conclusion of the study, the authors reported:

> No pathological effect whatever could be attributed to saccharin at levels of 1.0 percent or less. At 5 percent only one effect was noted, in the latter part of the experiment, namely an increased incidence of the ordinarily uncommon condition of abdominal lymphosarcoma. In the 5 percent group there were seven animals with lymphosarcomas; this number is not out of line with the incidence in comparable groups of rats, but the fact that in four of the seven rats abdominal as well as thoracic lymphosarcomas were present is unusual, since ordinarily the ratio is about 1 to 15-20. Three of these four combinations occurred in animals on experiment one hundred and two or more weeks.

In 1969, FDA pathologists reevaluated the findings from the Fitzhugh study (Ref.12). They concluded:

> The only effect of treatment during life was retardation of growth at 5 percent. In regard to pathological changes, our diagnoses of individual lesions were almost identical to those of Dr. Nelson. However, there were differences of opinion as to the role played by saccharin. Dr. Nelson stated in his 1951 report and also in the paper previously mentioned that the only pathological effect of saccharin was an increase in the incidence of the ordinary uncommon condition of abdominal lymphosarcoma. While we were not impressed by this, our examination of the written data and the microslides led us to conclude that saccharin had induced 2 lesions, and possibly a third. (1) Papillary excrescences from the papilla and papillo-calyceal junction of the kidney in 13 of the 17 rats with kidneys sections microscopically

of 5 percent, 2/18 at 1 percent, and 1/15 at 0.5 percent. The papillary excrescences were the result of edema, vascular congestion, leukocyte infiltration, and fibroblastic proliferation of the stroma, stratification of the normally simple cuboidal epithelium to the stratified cuboidal or transitional type, calcium deposition, and in a few instances, phlebothrombosis. (2) Increased cellularity of the bone marrow at 5 percent. (3) While we have presented evidence which suggests that saccharin may have increased the incidence of the malignant lung tumor, lymphosarcoma, which occurs spontaneously in the rat and was very common in FDA rats at the time this study was performed, the data are inconclusive. A consideration of this, the presence of the renal changes, and the lack of knowledge as to whether the urinary bladder was affected strongly suggest the need for another two-year experiment.

A second long-term test of saccharin by oral administration to rats was completed in 1959 by Lessel (Ref. 13). As in the earlier Fitzhugh study, rats were fed saccharin for 24 months at levels up to 5 percent of their diet. Twenty male and 20 female rats were used per group. Lessel included a positive-control group to determine the susceptibility of his rats to the development of this tumor type, which he felt resembled the lymphosarcomas noted by Fitzhugh et al. Lessel found this type of tumor among the various tumors noted in both controls and treated animals; however, he did not find the incidence of tumors in the rats to be altered by the presence of saccharin in the diet even at the highest level (5 percent) fed.

In 1969, a re-study of the urinary bladders of some rats from the Lessel study was undertaken; however, all of the rats were not examined and the procedure used in the fixing of the urinary bladders would not be regarded as adequate by qualified experts. On gross observation of the rats, bladder abnormalities were noted at all feeding levels. Five males and three females at the 5-percent level exhibited these abnormalities. The author concluded that saccharin promoted the formation of bladder stones which in turn led to the bladder lesions (Ref. 14).

In 1970, at the request of FDA, the previously described studies and other data on the safety of saccharin were evaluated by NAS/NRC. At the conclusion of its review, the Academy made the following recommendations:

> Long-term studies designed according to present-day protocols and including adequate investigation of effects on reproduction should be completed in at least two species. In view of the concern about effects on the kidney and urinary bladder, special attention should be given to pathological examination of these organs.

Based on the data available in 1970, the Ad-Hoc Subcommittee on Nonnutritive Sweeteners of the NAS Committee on Food Protection accepted 1 percent as a "no-effect" level of saccharin in the diets of rats and mice (Ref. 15).

Between 1970 and 1975, additional lifetime chronic feeding studies of saccharin were conducted in which the compound was fed to laboratory animals either at a single- or multiple-dose level. These studies were carried out in a variety of laboratory animals including rats, mice, and hamsters. Two of these modern studies yielded notable and troubling results. In both of these studies, diets containing saccharin were fed to male and female rats from weaning. At the proper age, these rats were bred and their offspring carried to lifetime. Thus, these offspring were exposed to saccharin in their diets from the time of conception until death. These two studies were conducted by FDA and in the laboratories of the Wisconsin Alumni Research Foundation (WARF).

The FDA study fed doses of 0.01, 0.1, 1, 5, and 7.5 percent saccharin to the laboratory animals. There were 50 males and 50 females in each dose group and 100 control animals (animals not fed saccharin). The study was terminated when the number of survivors in a test group fell to 20 percent of the starting number. Serial sacrifices were performed at 14 and 18 months. Of the 23 males fed the saccharin diet at the 7.5-percent level which were examined, 7 developed bladder tumors. No tumors were found at lower saccharin levels, but 1 of 25 males examined fed the control diet developed a bladder tumor. Of the female rats, bladder tumors were found in 2 of 31 examined animals fed the 7.5-percent diet. None were found in the control females nor in female rats fed the 5-percent or lower levels of saccharin.

The WARF study followed essentially the same protocol as the FDA study, except there were 20 males and 20 females per group and the study was terminated at 100 weeks. In the WARF test, bladder tumors were found in 7 of 15 male rats fed the diet containing 5 percent saccharin. No bladder tumors were found in the female rats at any level of saccharin feeding.

In the FDA study, the rats fed the higher dose levels (5.0 and 7.5 percent) tended to grow less well than did controls or those fed lower levels of saccharin; a body-weight deficit of about 15 percent prevailed throughout the test period. All other measurements of well-being were normal, however, including survival and organ weight/body weight ratios. In the WARF test, the high level (5 percent) saccarin-fed rats lagged behind the other groups during the period of rapid growth, but as adults revealed no difference in body weight. Indeed, the control group was the lightest among the males on test, but the weight range among the various groups was remarkably narrow.

The high dietary sodium (Na+) level introduced by feeding high levels (5 to 7.5 percent) of sodium saccharin (about 11 percent Na+) was taken into account in the FDA study by adding an equivalent level of Na+ as Na_2CO_3 to the diet of a group of rats fed the basal (no saccharin) diet. However, no test was made of Na+-free saccharin as opposed to soluble saccharin. This is an important issue, since, for example, the metabolic disposition of saccharin may be altered by higher Na+ levels; the question is not accounted for by the Na_2CO_3 control, nor is it clear whether carbonate is an appropriate anion for this particular study.

As previously explained, the rationale of animal testing for possible carcinogenic hazards to man contemplates maximizing the sensitivity of the bioassay system, requiring administration of the highest tolerable dose along with appropriate lower doses. Because saccharin has a low toxicity, dose levels as high as 5 to 7.5 percent of the diet were fed in the FDA and WARF studies. As of 1974, tumors had been associated with saccharin feeding only at these high levels and in only two of many studies—those conducted by FDA and by WARF. This result raised uncertainty as to whether saccharin itself was the carcinogen, or whether the bladder tumors were induced by an impurity in the saccharin (orthotoluenesulfonamide) that was present at a detectable dose when high levels of saccharin were fed.

In addition, the high levels of saccharin fed were thought to raise the problem of calculus formation (Ref. 16). Calculi were associated with the occurrence of bladder tumors in the study by Hicks et al., (Ref. 17). Orthotoluenesulfonamide is a carbonic anhydrase inhibitor which can increase urinary pH, predisposing to calculus formation. Clayson found that bladder tumors due to certain sulfonamides were eliminated by feeding NH_4Cl to give an acid urine (Ref. 18). Furthermore, saccharin alone may cause bladder calculi (Ref. 19). This was thought to be potentially important, because there is evidence that bladder stones may play a determining role in the appearance of bladder tumors in the rats. Occurrence of bladder stones and increased urinary pH associated with saccharin feeding were not investigated in the FDA or in the WARF study. It was thought that this phenomenon may be critical in the embryo or newborn rat that is exposed to saccharin.

It should be emphasized that in both the FDA and WARF tests the offspring (F_1) generation of rats, i.e., those that were conceived after the parental generation had been placed on the saccharin-containing diets, were held and observed for manifestation of toxicity. The relatively high sensitivity of experimental animals to transplacental exposure to carcinogens has become obvious in recent years (Ref. 20). A number of carcinogens have been shown to be effective at very low levels by the transplacental route. Frequently, exposure of the pregnant female is associated with the relatively early appearance of tumors in the offspring. Despite these important implications, information about transplacental carcinogenesis is limited. For example, the dose level to which the fetus is exposed is often unknown, nor is there an understanding of the importance of developmental state, metabolic capacity, immune competency, and factors related to fetal pharmacology.

Even with these uncertainties, however, the F_0—F_1 feeding procedure is considered to be an appropriate and essential test because saccharin may be consumed by pregnant women as well as individuals of all ages. The technique of in utero exposure in lifetime testing has been recommended by an expert on carcinogenesis of the FDA Advisory Committee on Protocols for Safety Evaluation, J. Tox. and Appl. Pharmacol. 20:419–438 (1971). The panel recognized that exposure of an animal to a chemical early in life, even during pregnancy, may be important in influencing expression of carcinogenesis later in life. The panel stated that "since one of the important purposes of the chronic toxicity tests is the detection of carcinogenic potential, it would seem desirable to begin the exposure as early in life, i.e., as close to conception as possible."

The International Agency for Research on Cancer of the World Health Organization (IARC Scientific Publications No. 4) has also endorsed the need to consider in utero exposure in the study of carcinogenesis potential. The IARC report noted that "experimental studies have indicated the increased susceptibility of neonatal animals to the carcinogenic insult. The logical development of studying the effect on the rodent fetus of maternal exposure to a chemical carcinogen has made it clear that this pathway could well be operative in the human fetus."

Unfortunately, in neither the WARF study nor the FDA study were the rats in the parent (F_0) generation continued for long-term carcinogenicity testing of saccharin; thus no comparative data on the susceptibility of F_0 and F_1 rats in an internally controlled experiment were obtained. Therefore, at the conclusion of these studies, doubt remained about whether the concurrence of transplacental exposure and of bladder tumors was causally related.

Because of the continuing questions about the carcinogenicity of saccharin, in June 1972, FDA once more called upon the Academy to review the results of all experiments on the issue. To be able to provide FDA with a complete and up-to-date report, the Academy delayed completing its review until several studies, including the FDA study, then underway, were completed.

The Academy's report was received by FDA in December 1974. The report's primary conclusion was that the data then available had "not established conclusively whether saccharin is or is not carcinogenic when administered orally to test animals." This conclusion was based in part on the uncertainty about the role of orthotoluenesulfonamide (OTS) in the induction of tumors. The Academy recommended that additional research on saccharin be conducted to determine whether saccharin is a carcinogen. The Academy recommended further that FDA reconsider the question when a substantial portion of the additional data became available.

E. CANADIAN STUDY

The recently reported Canadian study was initiated in February 1974 under the sponsorship of the Department of Health and Public Welfare of the Canadian Government (Toxicity and Carcinogenicity Study of Orthotoluenesulfonamide and Saccharin, Project E405/405E). Two generations of test animals (the F_0 and F_1 generations) were fed OTS and OTS-free saccharin to evaluate the toxicity and carcinogenicity of these compounds. The study on saccharin was the third experiment in which rats were exposed to saccharin during their period of development in the uterus and then throughout their entire life span. Both the earlier FDA and the WARF studies had shown an increased incidence of bladder tumors in male rats, but had left unresolved the question whether the tumors were caused by saccharin itself or by OTS. The Canadian study was designed to clarify this question by testing the OTS by itself as well as by testing purified saccharin containing only minimal amounts of the impurity. The Canadian study was thus designed to resolve the uncertainties noted by the NAS in its 1974 report.

Six groups of 50 male and 50 female rats were included in the study: a control group, 3 dose levels of OTS at 2.5, 25, and 250 milligrams per kilogram per day, a group receiving 5 percent saccharin (2,500 milligrams per kilogram per day) in the diet, and a group receiving 250 milligrams per kilogram OTS per/day and 1 percent ammonium chloride in the drinking water. The doses of OTS incorporated the amount of OTS, ranging from 0.6 to 27 milligrams per kilogram OTS per day, which may have been consumed by animals in the FDA and WARF studies on saccharin. OTS, a weak carbonic anhydrase inhibitor, may have a tendency to produce a slightly alkaline urine, possibly resulting in an increased incidence of bladder stones. Therefore, ammonium chloride was added to the drinking water of one OTS group to prevent this effect by producing a more acidic urine. The rats were observed daily, their weights and food consumption were recorded weekly, and 20 males of each generation of controls, saccharin-treated, and high-level OTS treated animals with and without ammonium chloride had urine examined at 6-month intervals for microscopic calculi and parasite eggs.

The results of the Canadian study have been evaluated by expert pathologists, including scientists from FDA and other institutions in the United States, from Great Britain, and from other European countries, as well as from Canada. The findings indicate unequivocally that saccharin causes bladder tumors in the test animals. Specifically, 7 male and no female rats in the F_0 generation developed bladder tumors. Twelve male and two female rats in the F_1 generation developed bladder tumors. Thus, of a total of 200 rats fed saccharine, 21 developed bladder tumors.

In sharp contrast, of 100 control animals—those not fed saccharine or OTS—only 1 developed a tumor. Moreover, the low incidence of tumors in the animals fed OTS clearly resolves the earlier speculations, based on the FDA and WARF studies, that OTS and not saccharin may have been responsible for the cancers in the test animals. No evidence of bladder parasites was found in any of the rats. Microscopic crystals were found in the urine but the distribution did not seem to be related to treatment. Two grossly visible bladder stones were found in rats bearing tumors, one receiving saccharin and the other receiving OTS, while six were found in animals of various groups without bladder tumors. There was no significant increase in bladder tumors in any of the group treated with OTS.

F. ASSESSMENT OF HUMAN RISK

An important question raised about the animal studies on saccharin is their relevance to human beings. Public reaction to recent publicity about the Canadian study suggests considerable misunderstanding about the nature of toxicity testing in animals and the interpretation of results. For example, it has been widely publicized that the dose of saccharin found to be carcinogenic in rats is about 1,000 times that ingested by a human in a single diet beverage (when both doses are adjusted for the difference in body weight between rats and humans). Since this amount of saccharin would clearly never be ingested chronically by any person, some have suggested that these results have no pertinence whatsoever to human risk. In the judgment of FDA, this conclusion is not valid for the reasons to be described in this section.

Before dealing with the saccharin data specifically, however, the principles of appraising the risk of chemical carcinogenic substances should be explicitly stated. Those principles are as follows:

1. Certain substances can be shown in validly controlled animal experiments to increase the incidence of benign and/or malignant tumors. This result does not occur with all chemicals, only with certain ones.

2. Those substances that cause benign or malignant tumors in one species often also do so in other species. Therefore, any substance that causes such tumors in any species must be considered a potential carcinogen in man.

3. Chemical carcinogens, like other toxic substances, generally demonstrate a dose-response relationship, i.e., the the greater the dose the greater the tendency to produce tumors, and vice versa. The predominant opinion among experts in the field of carcinogenesis is that the dose-response principle extends to very low doses of the carcinogen—that is, that there is no dose, however small, at which one can be certain there is no risk. In other words, there is no threshold dose below which a carcinogen may be considered safe in the absolute sense.

4. Estimation of the risk of a low dose of a carcinogen in animals requires that one test the carcinogen at a dose high enough to produce tumors in the group of animals tested and then calculate what the risk is likely to be at a very small dose. The intent of animal testing is not only to identify potential risks such as carcinogenesis but also to estimate whether such an effect is likely to occur with a frequency, e.g., of 1 in 100, 1 in

1,000, 1 in 10,000, 1 in a 100,000, 1 in a million, etc. Since the actual measurement of a single event once in, e.g., 1,000 times, requires several thousand animals, it is evident that direct measurement of low frequency events cannot feasibly be done because of limitations on cost, the difficulty of handling large numbers of animals, etc. The problem is thus currently solved, albeit imperfectly and not without difference of opinion among experts, by conducting tests with a feasible number of animals at high doses and extrapolating the results to low doses.

5. The method of extrapolation of results obtained at high doses to low doses should be a "conservative" method, i.e., it should err in the direction of overstating risk rather than understating it. Two accepted methods that meet this principle are the linear extrapolation method and the Mantel-Bryan procedure. In the dose range under consideration, the two methods give similar results for saccharin. The linear extrapolation method has been used in the FDA calculation on saccharin because it is easier to explain and understand.

6. The results of animal tests and their extrapolation to low doses provides an estimate of the risk of developing a tumor in the species tested. If one is to assume that such results are directly applicable to man, one must assume that one lifetime in the test animal is equal to a lifetime in man and that the test animal and humans are equally sensitive to the carcinogen. These assumptions are clearly open to debate, but in the absence of data to the contrary, the opinion of most experts is to assume that they are applicable. In the case of some carcinogens, wide variation among species in their sensitivity to the chemical has been demonstrated. The current view of experts is that these differences are due, at least in part, to species differences in the way the carcinogen is metabolized. In the case of saccharin, the drug is metabolized little, if at all, in either the rat or man. This fact supports the assumption that results from testing in rats are applicable to human risk assessment. The FDA risk estimates are then based on the principle that risk estimates in the rat are directly applicable to man.

Current scientific methods are not capable of determining the exact risk to humans of a chemical found to be carcinogenic in animals. However, techniques are available for estimating the upper limits of the risk. The Food and Drug Administration estimates that the lifetime ingestion of the amount of saccharin in one diet beverage per day results in a risk to the individual of somewhere between zero and 4 in 10,000 of developing a cancer of the bladder. If this risk is transposed to the population at large and if everyone in the United States drank one such beverage a day, this would result in anywhere between zero and 1,200 additional cases of bladder cancer per year. These estimates are identical to the estimates recently presented publicly by representatives of the Food and Drug Administration and of the National Cancer Institute (NCI) in hearings before the Health Subcommittee of the House Committee on Interstate and Foreign Commerce. The approach used in their calculation is described in the following paragraphs.

In the Canadian study, a 24 percent incidence of bladder tumors (12 of 50) was noted in the second generation male rats fed saccharin in a dose of 5 percent of the diet. This was the most sensitive group in the study to the carcinogenic effect of saccharin. Thus, in the absence of evidence that factors involved in its sensitivity are not relevant to the human population, this group is used to estimate the upper limit of human risk. There were no bladder tumors in an untreated control group of comparable size. Although the observed incidence of bladder tumors was 24 percent, the upper limit of risk in this study at the 95 percent confidence level is 36 percent. A 5 percent dietary level of saccharin in the rat is equivalent to 2,500 milligrams/kilogram/day of saccharin. If a 60-kilogram human (approximately 132 pounds) were to ingest 150 milligrams/day of saccharin (i.e., 2.5 milligrams/kilogram/day over a lifetime, he or she would thus receive the equivalent of one one-thousandth of the rat dose per day. This dose is approximately that contained in one large diet beverage drink (12½ ounces) per day.

Since rats fed 2,500 milligrams/kilogram/day may have as high as a 36 percent incidence of bladder tumors, ingestion by rats of one one-thousandth of that dose could yield, by linear extrapolation, an incidence of 0.036 percent or 4 cases per 10,000.

The lifetime risk of bladder cancer in humans in the United States is 1.5 percent; that is, of every 10,000 persons, it is expected that 150 will develop bladder cancer sometime during their lives. Extrapolating from the Canadian rat study, and if one assumes a direct correlation between the estimate of maximum risk of saccharin in rats and in humans, if a human ingests 150 milligrams/day of saccharin for a lifetime, he could increase the risk of bladder cancer by 0.036 percent, for a total risk of approximately 1.54 percent. That is, of every 10,000 persons, 154 might develop bladder cancer (if they all use 150 milligrams/day of saccharin) and if the assumptions are valid.

The risk from use of 150 milligrams/day of saccharin over a lifetime can be assessed in another fashion. The annual case rate of bladder cancer in the United States is given by the NCI as approximately 30,000. If everyone in the United States ingested 150 milligrams of saccharin per day (e.g., from one large diet drink) over a lifetime, and if the other assumptions are correct, there could be approximately an additional 1,200 cases per year (or an increase in risk of 4 percent over the basal risk). If only half the population ingested 150 milligrams of saccharin per day over a lifetime, an additional 600 cases per year could occur (or an increase in risk of 2 percent over the basal risk).

The estimated increase risk from this moderate use of saccharin cannot be detected in human epidemiological studies. Such studies usually can only detect increased risks of 200 to 300 percent (i.e., 2 to 3 times the baseline rate) or greater. Even the best feasible epidemiologic study is not likely to detect an increased risk of only 2 to 4 percent over background incidence. Thus, for example, the author of one epidemiological study of bladder cancer in consumers of artificial sweeteners (Kessler, I. I., J. Urology, 115:143–146, 1976) noted that "The sample sizes used here would permit the detection of an 80 percent increase in bladder cancer owning to nonnutritive sweetener use * * *." This study would not, then, have detected any increase in bladder cancer due to saccharin consumption if the risk is at the level suggested by the Canadian study in rats.

As discussed previously, cancer has a long latent period, requiring 5 to 30 years before it can be detected. Although saccharin has been used in food for over 70 years, it is only in the past 15 to 20 years that its use has become substantial. Thus, it is probably too early to ascertain from human epidemiological studies the number of bladder cancers associated with saccharin consumption. This conclusion was reached by the authors of one of the epidemiological studies on saccharin (Armstrong, B. and R. Doll, Brit. J. Prev. Soc. Med., 28:233–40, 1974) who pointed out that "If the minimum time necessary to see a significant number of bladder cancers induced by saccharin were more than thirty years * * * it would be too early to see an effect of saccharin consumption on mortality rates."

In a third epidemiological study on saccharin consumption (Armstrong, B. et al., Brit. J. Prev. Soc. Med., 30:151–157, 1976) only about 600 of the diabetics studied had consumed saccharin for more than 25 years. This number is far too low to detect the level of risk from saccharin consumption suggested by the experiments in rats. The fact that these epidemiological studies in patients with diabetes who used saccharin for prolonged periods revealed no detectable increased in bladder cancer is therefore compatible with the available animal data. A common feature of all three epidemiological studies is their comparative insensitivity, which could permit a sharply increased incidence of bladder cancer attributable to consumption of saccharin—on the order of more than 20,000 cases per year in the American population—to go undetected.

By contrast, the risk of lung cancer from cigarette smoking (which FDA has no authority to regulate) is now readily detectable in human epidemiological studies. However, even though cigarette smokers have been shown to incur a risk of developing lung cancer that is 500 to 2,000 percent greater than the risk of lung cancer incurred by nonsmokers, depending on how much they smoke, it took many years to recognize and document the increased risk. The first suggestions of an association between cigarette smoking and lung cancer were not made until the late 1930's (Müller, F. H., Z. Krebsforsch, 49:57–84, 1939). Several epidemiological studies reported an association between cigarette smoking and lung cancer in the early 1950's, but widespread acceptance of the relationship did not occur until publication of the 1964 report to the Surgeon General entitled Smoking and Health.

The Food and Drug Administration thus considers the animal data and the human epidemiological data on saccharin to be compatible. The estimated excess risk to the individual of developing bladder cancer from lifetime use of, e.g., 150 milligrams of saccharin per day, is believed to be somewhere between zero and 4 per 10,000. The estimated population risk in the United States, assuming such use by each individual, is somewhere between zero and 1,200 cases per year.

Although the risk from consumption of saccharin is small compared to that of other health hazards, e.g., cigarette smoking, saccharin is only one of a potentially large number of hazards present in our environment. The Commissioner believes that reduction of prolonged, general exposure to a number of weakly carcinogenic substances in our environment as they are discovered may be essential to reduce the total incidence of cancer.

6. LEGAL BASIS FOR ACTION

Press reports of the announcement of FDA's intention to withdraw approval of saccharin as an ingredient in foods and beverages have given the impression that the Commissioner is acting reluctantly, based exclusively on the Delaney anticancer clause of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 348 (c)(3)(A)) and, further, that the agency's action was triggered solely by the findings of the Canadian study. Neither impression is accurate.

As should be clear from the foregoing discussion, questions about the safety of saccharin have persisted almost from the date of its introduction. Serious doubt about its potential for causing cancer in laboratory animals arose much later, but this concern, too, is not new. Before the Canadian study, two scientifically sound and generally well-conducted studies had suggested an association between saccharin and bladder cancer in animals exposed to high doses of the sweetener. The Canadian study unequivocally confirms this association and lays to rest speculation that the causative agent may have been OTS. There can no longer be any doubt that saccharin causes a sharply increased incidence of bladder cancer in test animals.

The discussion in the previous section makes clear that the human risk of cancer indicated by these findings is significant and cannot be ignored. The Commissioner believes that conscientious protection of the public health is not consistent with continued general use in foods of a compound shown to present the kind of risk of cancer that has been demonstrated for saccharin—regardless of the asserted benefits of its use for some individuals in the population.

Section 409(c) of the act (21 U.S.C. 348(c)) requires that any food additive must be found to be safe for human consumption before it can be approved or, in case of an additive already approved, continue to be used in foods. Based on the accumulated evidence of hazard associated with ingestion of saccharin, culminated by the Canadian study, the Commissioner concludes that the finding required by the statute can no longer be made, and that the interim food additive regulation approving the use of saccharin should be repealed.

FDA has previously prohibited the use in food of ingredients found to cause cancer in laboratory animals to which the Delaney clause was not applicable. For example, in January 1950, before enactment of the Delaney clause, FDA prohibited the use in food of two artificial sweeteners as "poisonous substances." This conclusion was based in large part on the finding of liver tumors in rat studies. In May 1968, FDA prohibited the use in food of the flavoring agent, oil of calamus, based on a finding of carcinogenicity in animal studies. Oil of calamus had been used in food on the determination that it was generally recognized as safe; thus, the Delaney clause did not apply. There are a number of other examples. In short, although FDA has acted on a number of occasions to remove carcinogenic substances from the food supply during the past 25 years, only two previous actions—both involving minor indirect food additives—have been based on the Delaney clause.

Those actions, like this one, were based on certain well-recognized postulates about chemical carcinogenesis: (1) there is reason to believe that those substances which cause cancer in animals may also cause cancer in man; (2) animal tests, despite inadequacies, provide the best evidence currently available about the potential of chemicals to cause cancer in humans; (3) there is no reliable basis for concluding that there is a completely "safe" level of a carcinogen, i.e., a threshold level that will not cause cancer in some members of the population; and (4) cancer appears to be an irreversible process, in both test animals and in man.

It is of course true that the present law would afford the Commissioner no choice but to prohibit the marketing of saccharin as an ingredient in foods even if he were not persuaded that the scientific evidence independently warranted such action. The Delaney anticancer clause specifies that "[N]o additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal * * *." (21 U.S.C. 348 (c)(3)(A).) There can no longer be any question that saccharin does cause cancer when ingested by laboratory animals, in this instance in tests that the Commissioner would in any event regard as appropriate for the evaluation of carcinogenicity.

Therefore, under both the general safety requirement of the Food Additives Amendment of 1958 and the Delaney anticancer clause, the Commissioner concludes that saccharin may no longer be approved as a food additive. This proposal is issued to comply with the procedural requirements of section 409(h) of the act. The Commissioner welcomes comments on any facet of this proposal, including the reasonableness of his judgment about the safety of saccharin under the law. He feels constrained to point out, however, that the wisdom of the Delaney clause is not at issue in this proceeding. FDA could not ignore that provision even if the Commissioner were persuaded that the risks to human health were less than they appear. He further notes that under the provisions of the law relating to food additives, FDA is not empowered to take into account the asserted benefits of any food additive in applying the basic safety standard of the act.

The Commissioner does recognize, however, the potential medical value of permitting saccharin to remain available for individuals who may depend on a nonnutritive sweetener to maintain a diet free from sugar, provided such products can meet the standards of the drug provisions of the act. This subject is addressed in the following part of this preamble, on which the Commissioner specifically invites comments from specialists in the treatment of diabetes and obesity.

II. USE OF SACCHARIN IN DRUGS

A. HISTORY OF DRUG USE OF SACCHARIN

In addition to being used in foods, saccharin has been used in drugs for a number of years as a sweetening agent to improve the taste of oral drug products. Thus saccharin is used extensively in such drugs as pediatric liquid preparations, chewable tablets, and mouthwashes and toothpastes with drug claims. When used as a sweetener in a drug product, it is usually used in conjunction with a nutritive carbohydrate sweetener, such as sucrose or sorbitol, to mask the bitter aftertaste often experienced with saccharin. Saccharin is a pharmaceutical aid in liquid pediatric products where palatability is important to induce small children to take the medication. The volume of sucrose needed to provide acceptable levels of sweetness in some of these products has posed problems of incompatibility in the formulation in certain products.

The quantity of saccharin used as a flavoring agent in drug products covers a wide range. For example, of 12 penicillin V potassium products for oral suspension that were examined, the concentration of saccharin ranged from a low of 5.2 milligrams per teaspoonful to a high of 42.8 milligrams per teaspoonful. If a pediatric liquid oral preparation contains 40 milligrams of saccharin per teaspoonful (one dose) and the maxiusual daily dose is 2 teaspoonfuls four times a day, a child could consume 320 milligrams per day of saccharin from this one drug. Obviously, if other products containing saccharin were also being consumed, the daily intake of saccharin would be much higher. It should also be noted that drug products can be used for both the treatment of acute and chronic conditions. Thus, if a drug product containing saccharin is administered daily for the treatment or prophylaxis of a chronic condition, such as rheumatic fever, the patient could be exposed to a daily amount of saccharin equivalent to that contained in one or more diet soft drinks.

Saccharin is also marketed in tablet, powder, and liquid forms as a so-called "tabletop sweetener" for use in conditions in which nutritive carbohydrate sweeteners in the diet must be avoided. Certain of these products meet the statutory definition of a drug in that they are recognized by the U.S. Pharmacopeia or the National Formulary. In addition, they have at one time or another been tacitly recognized by FDA as drugs. In recent years, however, such products have been marketed and regulated as food additives.

In light of the recent Canadian study's unequivocal demonstration that saccharin causes malignant bladder tumors in test animals, the Commissioner has examined the use of saccharin in drug products, both as an inactive ingredient and as an active ingredient. In his judgment, the safety considerations involving the use of saccharin in drug products differ from those regarding its use in foods. Moreover, the Delaney clause does not apply to drug products. An ingredient that is clearly unjustified for general use in foods for humans may be suitable for use as a drug when there is a legitimate medical need that outweighs the risks of possible adverse effects. The Commissioner is thus permitted under the drug provisions of the law to evaluate the risk of using saccharin compared to the benefits of its use as a drug ingredient.

B. SACCHARIN AS AN INACTIVE INGREDIENT IN DRUG PRODUCTS

With respect to the use of saccharin as a pharmaceutical aid, the Commissioner has tentatively concluded that the risk of such use in most drug products is not outweighed by the benefits, and thus, saccharin will not be permitted as an inactive ingredient unless it affords an overriding benefit. The Commissioner therefore proposes to add new § 310.514 to Part 310 (21 CFR Part 310) of the new drug regulations, declaring that any drug product for human use containing saccharin as an inactive ingredient is a new drug and is misbranded unless such product is specifically exempted from the regulation. The Commissioner bases this proposal on the fact that the use of saccharin in most drug products as an inactive ingredient produces no direct therapeutic benefit. Thus, the possible risk associated with the use of saccharin for such purpose is medically unjustified. This is particularly true because individuals do not have the opportunity to choose whether or not to take such a risk if saccharin were to remain available as an inactive ingredient in drug products.

In § 310.514, the Commissioner proposes that any holder of an approved new drug application for a drug product containing saccharin as an inactive ingredient be required to submit to FDA within 9 months of the date of publication of the final regulation, a supplemental application providing for a new revised formulation removing saccharin as an ingredient. The revised formulation may not be marketed before the receipt of written notice of approval of the supplemental application by FDA. Any sponsor of a "Notice of Claimed Investigational Exemption for a New Drug" (IND notice) for a drug product containing saccharin as an ingredient shall amend the IND notice within 9 months of the date of publication of the final regulation to revise the formulation removing saccharin as an ingredient. Under the proposal, the Commissioner would initiate action to withdraw approval of an application or terminate an IND notice if any current holder of an approved new drug application or sponsor of an IND notice fails to submit a supplemental application or to amend an IND notice as set forth, and within the time periods provided for, in § 310.514.

A period of 9 months for the submission of supplemental applications is being proposed to allow manufacturers time to reformulate their products and perform the stability and bioavailability studies, where necessary. Depending upon the type of product, i.e., tablet or liquid, and the amount of saccharin currently in the product, reformulation to maintain palatability may pose problems. For example, attempts to raise the content of nutritive sweeteners to mask the bitter taste of a drug is limited by such physical factors as solubility. Further, because of the increased nutritive sweetener content, a preservative may have to be added. Likewise, as of July 7, 1977, firms, will also have to comply with the bioavailability requirements as set forth in §§ 320.21 and 320.22 (21 CFR 320.21 and 320.22) of the regulations. Similar provisions, applicable to antibiotic drug products, are set forth in a new § 430.300 that the Commissioner proposes to add to Part 430 (21 CFR Part 430) of the regulations.

Because of the potential need for specially formulated drugs for diabetics or for special situations in which saccharin may be necessary for the product as a pharmaceutical aid, the Commissioner is also proposing a specific provision under which a petition may be submitted to FDA requesting that a specific use of saccharin as an inactive ingredient be permitted. To support such a petition, the person requesting the exemption must submit the following information: (1) the amount of saccharin in the drug product; (2) is saccharin is included as a pharmaceutical aid, an adequate showing that there are no technically feasible alternatives to saccharin, or an adequate showing that the drug product containing saccharin provides a substantial health benefit that would not be available without the use of saccharin, for example, the product is one specifically formulated for diabetics; and (3) copies of the proposed labeling specifying the saccharin content.

Whether or not the drug product is subject to the requirements for an approved new drug application or for antibiotic certification, under the proposal, a drug product containing saccharin as an inactive ingredient shall, unless exempted, not be manufactured after 18 months and shall not be initially shipped into interstate commerce 18 months from the date the final regulations are published in the FEDERAL REGISTER. Initial introduction into interstate commerce of a drug product for purposes of this regulation means the first shipment of the final dosage form of the drug product into interstate commerce pursuant to a sale or consignment to an independent party. Since these dates are applicable to all drug products, firms submitting supplemental new drug applications or amendments to antibiotic drug files should assure that they are complete when they are submitted.

C. SACCHARIN AS A SINGLE-ACTIVE-INGREDIENT DRUG

Saccharin has been available for many years in single-active-ingredient products for use by individuals who must control their caloric intake. These products consist of tablets, liquids, or powders containing saccharin as the primary sweetening ingredient, and some are popularly known as "tabletop sweeteners." For the most part, these products have been regulated by the agency as food additives, and most recently as special dietary foods (see 21 CFR 105.79, formerly 21 CFR 125.7 prior to recodification published in the FEDERAL REGISTER of March 15, 1977 (42 FR 14302)).

These products have also historically been recognized as drugs. The Referee Board of the United State Department of Agriculture, while considering the safety of saccharin in foods in 1912, stated, "The Food and Drug Act provides that any substance which is intended to be used for the prevention, cure, or mitigation of disease is a drug, and a product containing saccharin and plainly labeled to show that the mixture is intended for the use of those persons who, on account of disease, must abstain from the use of sugar, falls within the class of drugs * * *." This statement by a board of scientific advisors indicates that, even as early as 1912, saccharin was recognized as a drug when offered for sale for use by persons with a medical need to limit nutritive sweeteners in their diets.

The United States Pharmacopeia has recognized saccharin as a pharmaceutical aid since at least 1926. The current edition of the National Formulary recognizes saccharin calcium, saccharin sodium, and saccharin sodium tablets. By virtue of the recognition of those products in the official compendia, and depending on their labeling, they may fall within the definition of "drug" in section 201(g) of the act (21 U.S.C. 321(g)).

Saccharin was reviewed in the mid-1960's under the new drug provisions of the act as an active ingredient of a new drug product in combination with a cyclamate salt, but the new drug application for this product is no longer approved. In addition, as recently as August 27, 1975 (40 FR 38179), FDA published an amended notice requesting data and information on saccharin for review by its OTC Miscellaneous Internal Products Panel. This publication was a part of the agency's ongoing review of OTC drug products for human use currently marketed in the United States. Saccharin was included in the listing of ingredients under the product categories of sweeteners and weight control products. The Commissioner notes, however, that in response to the August 27, 1975 notice, no submissions of any type were made for any product containing saccharin as an active ingredient. The Bureau of Drugs of FDA thus has no request before it at the present time from any manufacturer to market saccharin either OTC or by prescription, under the OTC review or as a new drug.

Although single-ingredient tabletop sweeteners containing saccharin in the form of tablets, liquids, or powders have been subject to regulation as foods, the Commissioner believes that such products may be considered as drugs, depending upon the claims made for them. The essential criterion for determining whether a product is a drug is whether it meets the definition in section 201(g) (1) (B) and (C) of the act, as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of a disease in man or other animals," and "articles (other than food) intended to affect the structure or any function of the body of man or other animals."

Once determined to be a drug, a product must meet the standards of the drug provisions of the act, among them the safety and effectiveness requirements of either section 201(p) or 505. Section 201(p) states that a drug is a new drug if it is "not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof." If a new drug, the law requires among other things "substantial evidence that [it] will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof" (21 U.S.C. 355(d)(5)). Such substantial evidence means "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof" (21 U.S.C. 355(d)(5)).

Finally, if a drug is otherwise marketable, the Commissioner must determine whether it should be considered as a prescription or OTC drug. The applicable standard (21 U.S.C. 353(b)(1)(B)) requires that a drug must be dispensed by prescription if, "because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, [it] is not safe for use except under the supervision of a practitioner licensed by law to administer such drug."

The Commissioner recognizes that saccharin is the only product available on the market for use as a nonnutritive sweetener and that such use may be important to the proper dietary management of individuals who must control their intake of nutritive sweeteners. These include individuals with conditions such as diabetes, obesity, reactive hypoglycemia, and carbohydrate-induced hyperlipemia. Whether such use is properly construed as a drug use under the law depends upon the claims made by the manufacturer and is reasonably open to debate. The Commissioner is prepared to consider the possibility that such single-ingredient sweeteners may be marketable as drugs, even if the same formula might not be approvable as a food additive. The Commissioner believes, however, that the proper context for considering such a use under the drug laws is in reviewing new drug applications for individual products.

In reaching this tentative conclusion, the Commissioner has specifically excluded the possibility of reviewing the matter further as part of the OTC review. This review is fundamentally intended to identify those conditions under which specific ingredients can be generally recognized as safe and effective for OTC use within the meaning of section 201(p) of the act. There is no realistic prospect, however, that such a determination can be made for saccharin as a drug. Saccharin has no history of marketing in the United States as a drug approved for effectiveness under the Drug Amendments of 1962; general recognition of effectiveness under these conditions would seem to be precluded, even though effectiveness vel non may be demonstrated. Similarly, the Canadian study represents new evidence reflecting on the safety of the product which the Commissioner considers sufficient to remove it from the market as an approved food additive. In the face of this new evidence, general recognition of safety does not appear to be a reasonable possibility. For these reasons, the Commissioner concludes that saccharin is not a suitable ingredient for review by the Miscellaneous Internal Products Panel of the OTC Review, and the call of August 27, 1975 for submission of information on sweeteners to this panel is hereby rescinded.

The Commissioner believes that the new drug application is a more appropriate mechanism for considering the issues related to the marketability of saccharin-containing sweeteners for use by individuals who for medical reasons must limit their intake of nutritive sweeteners. He therefore invites comment on a proposal to add a new § 310.514(b) to the regulations which would permit the submission of new drug applications for such products. This authorization would be limited to consideration of tabletop sweeteners in packaging appropriate for use by individual patients. The agency will not entertain under this proposal new drug applications for any products that are clearly foods sweetened with saccharin, e.g., diet soft drinks, canned fruits, etc.

The proposed regulation requires that any manufacturer wishing to ship a single-active-ingredient sweetener containing saccharin in interstate commerce would have to meet the following conditions after publication of the final regulations:

1. Within 180 days, submit a new drug application for the product, meeting the requirements of § 314.1 of the regulations.

2. Within 120 days, label the product with the following interim indications statement: "For use as a noncaloric sweetener when a sugar-restricted diet is medically indicated, as in patients with diabetes" and with a warning statement concerning the risk of cancer. The Commissioner proposes the following warning statement, and solicits additional suggestions: "Warning: Saccharin causes bladder cancer in animals. Use of saccharin may increase your risk of cancer."

Any manufacturer not meeting these conditions would be subject to regulatory action.

The Commissioner proposes that those manufacturers whose products meet the requirements of this section will be permitted to market their products while their new drug applications are under review. Such marketing is permitted for a marketed drug which is newly declared as a new drug provided the Commissioner determines it is or may be medically necessary (*Hoffman-LaRoche, Inc. v. Weinberger*, 425 F. Supp. 890 (D.D.C. 1975)). The Commissioner has determined that the continued marketing of saccharin as a single-ingredient drug meets this criterion, at least for purposes of permitting further consideration of the data and information in new drug applications, since saccharin is the only remaining sweetener on the market for patients on sugar-restricted diets.

The foregoing determinations should in no way be construed as committing the Commissioner to approve any new drug applications submitted either for the interim indication proposed or any other indication. Approval will depend on whether the products as labeled meet the definition of a drug and whether the evidence presented in these applications meets the criteria for approval set forth in the statute and in the regulations.

The Commissioner tentatively concludes that, if saccharin-containing sweeteners are labeled as drugs and if they are deemed to be otherwise approvable under the new drug provisions of the act, they may be marketed OTC. This conclusion is based on the lack of toxicity (other than risk of cancer, for which it will be labeled), the lack of other collateral measures necessary for its safe use, which would require a prescription, and the long history of safe OTC use of the product without a physician's prescription. The Commissioner invites comments on this tentative conclusion.

III. Use of Saccharin as a Cosmetic Ingredient

Saccharin is currently used as an ingredient in a number of cosmetic products, principally to affect taste. Many of these products, such as dentifrices (toothpastes) and mouthwashes, as well as lipsticks, are likely to be ingested under normal conditions of use. Although the risk of exposure to significant amounts of saccharin from any of these products may not be large, the use of saccharin affords no benefit sufficient to warrant the acceptance of any increased risk. The Commissioner therefore proposes to determine that the use of saccharin in any cosmetic product that is likely to be ingested and which is manufactured more than 30 days after the date of publication of a final regulation will result in the product being deemed to be adulterated under section 601(a) of the act (21 U.S.C. 361(a)).

IV. Use of Saccharin in Standardized Foods

Saccharin is listed as a mandatory ingredient in nine standards of identity for artificially sweetened fruit products. In addition two standards, 21 CFR 146.111 and 146.121 (formerly 21 CFR 27.128 and 27.103, prior to recodification published in the Federal Register of March 15, 1977 (42 FR 14302)) list as a mandatory ingredient "one or more of the artificial sweetening ingredients listed in and complying with Parts 170 through 129 of this chapter."

The Commissioner proposes to amend those standards of identity for artificially sweetened fruit products that require saccharin to be used as the artificial sweetener by deleting the reference to saccharin and replacing it with more general language requiring the use of "one or more of the artificial sweeteners listed in and complying with Parts 170 and 189" of Chapter I of Title 21 of the Code of Federal Regulations.

When the ban on saccharin as a food additive takes effect, the marketing of the foods covered by the 11 standards will be unlawful. The Commissioner has opted to amend the standards rather than revoke them to conserve agency resources.

If the standards were revoked and an artificial sweetener was subsequently approved for use by FDA, the process of establishing standards for artificially sweetened fruit products would have to begin anew. By keeping the standards on the books, the Commissioner will avoid unnecessarily expending scarce agency resources. The Commissioner emphasizes, however, that his election of the amendment approach rather than revocation should not be taken to be an implied prediction that FDA will soon approve another artificial sweetener as a replacement for saccharin. The amendments are being proposed as a matter of administrative convenience, not as a harbinger of future approval of any artificial sweetener.

V. Use of Saccharin in Animal Drugs and Animal Feed

The use of saccharin as an ingredient in animal drugs or animal feed for food-producing animals requires a demonstration that no residue will be found in food from the edible products derived from those animals, either by an assay designated in accordance with the provisos to the anticancer clauses of the act (sections 409(c)(3)(A), 512(d)(1)(H), and 706(b)(5)(B)) if it is a carcinogen, or by an assay designated under sections 409(b)(2)(D), 512(b)(7), and 706(b)(5)(A)(iv), in accordance with the general safety provisions of the act. No such assay has been submitted, nor, to the knowledge of the Commissioner, does such an assay exist. Accordingly, the Commissioner proposes to ban saccharin for all uses in food-producing animals.

Since saccharin is also an ingredient in some animal drugs and feeds intended for use in non-food-producing animals, the Commissioner proposes to disapprove this use as well. Saccharin provides no therapeutic benefit to animals and has not been shown to provide any overriding benefit to a measurable animal treatment population. For these reasons, the Commissioner concludes that any risks to animals from the use of saccharin in such drugs outweigh any theoretical benefit alleged from its continued use.

VI. Compliance Policy

An important aspect of this proposal is, quite obviously, the compliance policy that FDA intends to adopt as part of the final regulations on saccharin. Matters of interest to consumers and manufacturers and users of saccharin alike are: When will the ban take effect? Will it apply to manufacture or shipment of saccharin containing foods? Is a recall contemplated? When must new drug applications be submitted? This section summarizes FDA's intended compliance policy when final regulations are issued.

A. SACCHARIN USED IN FOOD

Under section 409(e) of the act (21 U.S.C. 348(e)), the final regulation revoking the interim food additive regulation for saccharin (21 CFR 180.37) shall be effective on publication in the Federal Register. The Commissioner intends, in the final regulation, to prohibit the addition of saccharin to any food (e.g., soft drinks) after the effective date of the final regulation. Foods that have been fully processed and packaged for sale to consumer or institutions on the effective date of the final regulation would be permitted to be sold. The addition of saccharin in the manufacture of food, further processing, or repacking, after the effective date of the final regulation will cause such products to be adulterated within the meaning of the act and subject to regulatory action.

B. SACCHARIN USED IN HUMAN DRUGS

When a final regulation is issued, holders of approved new drug applications for a drug product containing saccharin as an inactive ingredient and sponsors of IND notices for a drug product containing saccharin as an ingredient will have 9 months to file a supplemental application (NDA) or amendment (IND notice) to revise the formulation removing saccharin as an ingredient. Similar requirements are proposed for antibiotic drug products.

Petitions may be submitted to FDA requesting that a specific use of saccharin as an inactive ingredient be permitted. Such a petition must include the information specified in section II.B. of this preamble.

Manufacture of any drug products containing saccharin as an inactive ingredient would be prohibited after 15 months from the date of publication of final regulations in the Federal Register. Initial shipment of drug products containing saccharin as an inactive ingredient would be prohibited 18 months after the date of publication of final regulation in the Federal Register.

This proposal invites comment on the appropriateness of permitting the marketing of saccharin as a single-ingredient drug for use by persons who must restrict their intake of sugar, available without a physician's prescription. If the final regulation should permit such marketing, any manufacturer wishing to ship in interstate commerce a saccharin-containing tabletop sweetener would, within 180 days after the date of publication of the final regulation, have to submit a new drug application for the product and comply with the other requirements set forth in proposed § 310.514.

Tabletop sweeteners currently being marketed would be permitted to continue to be marketed as over-the-counter drugs, pending review and action on the new drug applications. The Commissioner cautions against substantial changes in the packaging format of saccharin as a single-ingredient product during this period. Within 120 days after publication of the final regulation, however, those products would have to be labeled with the statements prescribed in § 310.514(b)(2).

C. SACCHARIN USED IN COSMETICS

A final regulation prohibiting the use of saccharin in cosmetics that are likely to be ingested will be effective 30 days after publication of a final regulation in the Federal Register. The addition of saccharin to cosmetics that are likely to be ingested after the effective date of a final regulation would be prohibited. Cosmetics containing saccharin that are already on the market and those products that are fully processed and packaged for sale to consumers or institutions before the final regulation takes effect will be permitted to be sold. The prohibition on saccharin in cosmetics does not apply to products that are not likely to be ingested (e.g., hair tonics).

D. SACCHARIN USED IN ANIMAL DRUGS AND FEED

The final regulation prohibiting the use of saccharin in animal feed will be effective on publication in the FEDERAL REGISTER. The Commissioner intends, in the final regulation, to prohibit the addition of saccharin to any animal feed after the effective date of the regulation.

The final regulation prohibiting the use of saccharin in animal drugs will be effective 30 days after publication in the FEDERAL REGISTER. After the effective date, it will be unlawful to manufacture an animal drug containing saccharin. Holders of approved new animal drug applications for products that contain saccharin as an inactive ingredient will be required to file a supplemental application within 9 months of publication of final regulations.

E. RECALL OF SACCHARIN-CONTAINING PRODUCTS

The Commissioner has concluded that the protection of the public health does not require the recall from the market of food, drugs (human and animal), animal feed, and cosmetics that contain saccharin or the destruction of products that are fully processed and packaged for sale to consumers or institutions when a final regulation is issued. Thus, at this time, no recall is contemplated and products that contain saccharin on the market or fully processed and packaged for sale to consumers or institutions when a final regulation is issued would be permitted to be sold.

As discussed earlier in this preamble, the Commissioner believes that prolonged consumption of saccharin in ordinary foods, such as soft drinks, and exposure to saccharin from other products (i.e., drugs, animal drugs and feed, and cosmetics) poses a significant risk of cancer and should not be permitted in the future. However, the potential risk of human cancer from saccharin is cumulative; though significant, it is not immediate in the sense that the exposure of consumers to saccharin must be halted at once. The relatively short period of time in which products containing saccharin already on the market will be sold, does not, in the Commissioner's judgment, significantly threaten the public health.

The Commissioner emphasizes, however, that there is a significant potential risk of cancer from prolonged consumption of saccharin. His judgment is that a recall—with all the attendant costs to the industry and consumers—is not required to protect the public health; but this judgment should not be construed as reflecting a lack of concern about the cumulative risk associated with the routine consumption of saccharin by the general population.

All FDA regulations concerning human food were reorganized under Subchapter B—Food for Human Consumption, published in the FEDERAL REGISTER of March 15, 1977 (42 FR 14302). For the convenience of the reader, the following table lists the former designation of the sections in recodified Subchapter B which would be amended by this proposal.

New section:	Old section
145.116	27.16
145.126	27.24
145.131	27.73
145.136	27.40
145.171	27.6
145.176	27.34
145.181	27.57
146.111	27.120
146.121	27.103
150.141	29.4
150.161	29.5
172.130	121.1036
172.820	121.1185
180.37	121.4001
189.186	121.106(d)

The Commissioner has carefully considered the environmental effects of the proposed regulation and, because the proposed action will not significantly affect the quality of the human environment, has concluded that an environmental impact statement is not required. A copy of the environmental impact assessment is on file with the Hearing Clerk, Food and Drug Administration.

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Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(s), 301, 401, 402, 409, 502, 505, 512, 601(a), 701 (a) and (e), 52 Stat. 1042–1043 as amended, 1046–1047 as amended, 1050–1055 as amended, 70 Stat. 919, 72 Stat. 1784–1788 as amended, 82 Stat. 343–351 (21 U.S.C. 321(s), 331, 341, 342, 348, 352, 355, 360b, 361(a), 371 (a) and (e))) and under authority delegated to the Commissioner (21 CFR 5.1), it is proposed that Chapter I of Title 21 of the Code of Federal Regulations be amended as follows:

PART 145—CANNED FRUITS

1. In Part 145:

a. By revising § 145.116(a) to read as follows:

§ 145.116 Artificially sweetened canned apricots.

(a) Artificially sweetened canned apricots is the food which conforms to the definition and standard of identity prescribed for canned apricots by § 145.115(a), except that in lieu of a packing medium specified in § 145.115(a)(3), the packing medium used is water sweetened with one or more of the artificial sweeteners listed in and complying with Parts 170 through 189 of this chapter. Such packing medium may be thickened with pectin and may contain any mixture of any edible organic salt or salts and any edible organic acid or acids as a flavor-enhancing agent, in a quantity not more than is reasonably required for that purpose.

* * * * *

b. By revising § 145.126(a) to read as follows:

§ 145.126 Artificially sweetened canned cherries.

(a) Artificially sweetened canned cherries is the food which conforms to the definition and standard of identity prescribed for canned cherries by § 145.125(a), except that in lieu of a packing medium specified in § 145.125(a)(3), the packing medium used is water sweetened with one or more of the artificial sweeteners listed in and complying with Parts 170 through 189 of this chapter. Such packing medium may be thickened with pectin and may contain any mixture of any edible organic salt or salts and any edible organic acid or acids as a flavor-enhancing agent, in a quantity not more than is reasonably required for that purpose.

* * * * *

c. By revising § 145.131(a) to read as follows:

§ 145.131 Artificially sweetened canned figs.

(a) Artificially sweetened canned figs is the food which conforms to the definition and standard of identity prescribed for canned figs by § 145.130, except that in lieu of a packing medium specified in § 145.130(c), the packing medium used is water sweetened with one or more of the artificial sweeteners listed in and complying with Parts 170 through 189 of this chapter. Such packing medium may be thickened with pectin and may contain any mixture of any edible organic salt or salts and any edible organic acid or acids as a flavor-enhancing agent, in a quantity not more than is reasonably required for that purpose.

* * * * *

d. by revising § 145.136(a) to read as follows:

§ 145.136 Artificially sweetened canned fruit cocktail.

(a) Artificially sweentened canned fruit cocktail is the food which conforms to the definition and standard of identity prescribed for canned fruit cocktail by § 145.135(a), except that in lieu of a packing medium specified in § 145.135(a)(3), the packing medium used is water sweetened with one or more of the artificial sweeteners listed in and complying with Parts 170 through 189 of this chapter. Such packing medium may be thickened with pectin and may contain any mixture of any edible organic salt or salts and any edible organic acid or acids as a flavor-enhancing agent, in a quantity not more than is reasonably required for that purpose.

* * * * *

e. By revising § 145.171(a) to read as follows:

§ 145.171 Artificially sweetened canned peaches.

(a) Artifically sweetened canned peaches is the food which conforms to the definition and standard of identity prescribed for canned peaches by § 145.170(a), except that in lieu of a packing medium specified in § 145.170(a)(3), the packing medium used is water sweetened with one or more of the artificial sweeteners listed in and complying with Parts 170 through 189 of this chapter. Such packing medium may be thickened with pectin and may contain any mixture of any edible organic salt or salts and any edible organic acid or acids as a flavor-enhancing agent, in a quantity not more than is reasonably required for that purpose.

* * * * *

f. By revising § 145.176(a) to read as follows:

§ 145.176 Artificjally sweetened canned pears.

(a) Artificially sweetened canned pears is the food which conforms to the definition and standard of identity prescribed for canned pears by § 145.175(a) except that in lieu of a packing medium specified in § 145.175(a)(3), the packing medium used is water sweetened with one or more of the artificial sweeteners listed in and complying with Parts 170 through 189 of this chapter. Such packing medium may be thickened with pectin and may contain any mixture of any edible organic salt or salts and any edible organic acid or acids as a flavor-enhancing agent, in a quantity not more than is reasonably required for that purpose.

* * * * *

g. By revising § 145.181(a) to read as follows:

§ 145.181 Artificially sweetened canned pineapple.

(a) Artificially sweetened canned pineapple is the food that conforms to the definition and standard of identity prescribed for canned pineapple by § 145.180(a), except that in lieu of a packing medium specified in § 145.180(a)(2), the packing medium used is water sweetened with one or more of the artificial sweeteners listed in and complying with Parts 170 through 189 of this chapter. Such packing medium may be thickened with pectin.

* * * * *

PART 150—FRUIT BUTTERS JELLIES, PRESERVES, AND RELATED PRODUS

2. In Part 150:

a. By revising § 150.141(c) to read as follows:

§ 130.141 Artificially sweetened fruit jelly.

* * * * *

(c) The artificial sweetening ingredients referred to in paragraph (a) of this section are one or more of the artificial sweeteners listed in and complying with Parts 170 through 189 of this chapter.

* * * * *

b. By revising § 150.161(c) to read as follows:

§ 150.161 Artificially sweetened fruit preserves and jams.

* * * * *

(c) The artificial sweetening ingredients referred to in paragraph (a) of this section are one or more of the artificial sweeteners listed in and complying with Parts 170 through 189 of this chapter.

* * * * *

PART 172—FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION

3. In Part 172:

§ 172.135 [Amended]

a. By amending § 172.134 Disodium EDTA by deleting paragraph (b)(3).

b. By amending § 172.812 by revising paragraphs (b) and (c) to read as follows:

§ 172.812 Glycine.

* * * * *

(b) The additive is used or intended for use as a stabilizer in mono- and diglycerides prepared by the glycerolysis of edible fats or oils in an amount not to exceed 0.02 percent of the mono- and digylcerides.

(c) To assure safe use of the additive, in addition to the other information required by the act, the labeling of the additive shall bear adequate directions for the use of the additive in compliance with the provisions of this section.

§ 172.820 [Amended]

c. By amending § 172.820 Polyethylene glycol (mean molecular weight 200–9,500), by deleting and reserving paragraph (c)(2).

PART 180—FOOD ADDITIVES PERMITTED IN FOOD ON AN INTERIM BASIS

§ 180.37 [Revoked]

4. In Part 180, by revoking § 180.37 Saccharin, ammonium saccharin, calcium saccharin, and sodium saccharin, which had permitted saccharin and its salts in food on an interim basis pending additional study.

PART 189—SUBSTANCES PROHIBITED FROM USE IN HUMAN FOOD

5. In Part 189, by adding new § 189.185 to read as follows:

§ 189.185 Saccharin and its salts.

(a) The food additive saccharin is the chemical, 1,2-benzisothiazolin-3-one-1, 1-dioxide ($C_7H_5NO_3S$). Ammonium saccharin, calcium saccharin, and sodium saccharin are produced by the additional neutralization of saccharin with the proper base to yield the desired salt. Saccharin and the named salts have been used as sweetening agents in food.

(b) Food containing any added saccharin or saccharin salt is deemed to be adulterated in violation of the act.

PART 310—NEW DRUGS

6. In Part 310, by adding new § 310.514 to read as follows:

§ 310.514 Saccharin; use as an ingredient in drug products.

(a) Saccharin has been used for many years as a flavoring agent in drug products, such as pediatric liquid oral preparations, cough sirups, chewable tablets, and toothpaste with medical claims. Saccharin has also been used in the management or mitigation diabetes and other conditions in which the available carbohydrate and/or calories of a patient must be controlled. Information now available demonstrates that saccharin causes malignant bladder tumors in test animals and therefore has a potential for causing cancer in humans. The potential risk in humans outweighs the benefits of nontherapeutic use of saccharin. On the basis of this new evidence, saccharin has not been shown to be safe for use as an inactive drugs ingredient, with certain exceptions as provided for in paragraph (f) of this section.

(b)(1) Any drug product that contains saccharin, or one of its salts, as a single-active-ingredient product in liquid, tablet or powder form for use as a tabletop sweetener is a new drug within the meaning of seciton 201(p) of the act and requires an approved new drug application for marketing.

(2) Such products currently being marketed may remain on the market as over-the-counter products: *Provided*, (i) A new drug application complying with the requirements of § 314.1 of this chapter is submitted within 180 days of the date of publication of a final regulation; (ii) All products labeled after (120 days after date of publication of a final regulation) shall have the following statements displayed prominently on the principal display panel and on any other labeling, unless revised upon approval of the new drug application:

(A) "For use as a noncaloric sweetener when a sugar-restricted diet is medically indicated, as in patients with diabetes."

(B) "Warning: Saccharin causes bladder cancer in animals. Use of saccharin may increase your risk of cancer."

(C) Any drug product that contains saccharin as an inactive ingredient is a new drug within the meaning of section 20(p) of the act and is misbranded and subject to regulatory action under sections 301, 502, and 505 of the act.

(D) Any holder of an approved new drug application for a drug product containing saccharin as an inactive ingredient shall submit to the Food and Drug Administration on or before (9 months after date of publication of final regulation) a supplemental application providing for a revised formulation removing saccharin as an ingredient.

(1) The supplemental application shall contain:

(i) A full list of articles used as components and a full statement of the composition of the drug product.

(ii) Data showing that the change in composition does not interfere with any assay or other control procedures used in manufacturing the drug product, or that the assay and other control procedures are revised to make them adequate.

(iii) Data to establish that the stability of the product is not adversely affected by the revised formulation. If the data are too limited to support a conclusion that the drug will retain its declared potency for a reasonable marketing period, a commitment from the applicant:

(A) To test the stability of marketed batches at reasonable intervals;

(B) To submit the data as they become available; and

(C) To recall from the market any batch found to fall outside the approved specifications for the drug.

(2) The revised formulation shall not be marketed before the receipt of written notice of approval of the supplement by the Food and Drug Administration.

(e) Any sponsor of a "Notice of Claimed Investigational Exemption for a New Drug" (IND) for a drug product containing saccharin as an inactive ingredient shall amend the IND notice before (9 months after date of publication of final regulation) to provide for a revised formulation removing saccharin as an ingredient.

(f) If the holder of an approved new drug application or sponsor of an IND notice fails to comply with the provisions of paragraph (d) or (e) of this section, the Commissioner will initiate action to withdraw approval of the application or terminate the IND notice in accordance with the applicable provisions of section 505 of the act and Parts 312 and 314 of this chapter.

(g) Any person may file a petition in accordance with Part 10 of this chapter to amend paragraph (c) of this section to specify a use of saccharin in a drug product as not being subject to the misbranding provisions of that paragraph. The petition must be supported by the following information:

(1) The amount of saccharin contained in each dose of the drug;

(2) An adequate showing that there are not technically feasible alternatives to the use of saccharin in the drug product, or an adequate showing that the drug product provides a substantial health benefit or other public benefit that would not be available without the use of saccharin; and

(3) A copy of the proposed labeling clearly specifying the saccharin content and its intended use.

PART 430—ANTIBIOTIC DRUGS; GENERAL

7. In Part 430, by adding new Subpart F—Ingredients No longer Shown To Be Safe, consisting at this time of § 430.300, to read as follows:

Subpart F—Ingredients No Longer Shown To Be Safe

§ 430.300 Saccharin; use as an ingredient in antibiotic drug products.

(a) Saccharin has been used for many years as a flavoring agent in drug products, such as pediatric liquid oral preparations, cough sirups, chewable tablets, and toothpaste with medical claims. Saccharin has also been used in the management or mitigation of diabetes and other conditions in which the available carbohydrate and/or calories of a patient must be controlled. Information now available demonstrates that saccharin causes malignant bladder tumors in test animals and has a potential for causing cancer in humans. The potential risk in humans outweighs the benefits of nontherapeutic use of saccharin. On the basis of this new evidence, saccharin has not been shown to be safe for use as an inactive drug ingredient, with certain exceptions as provided for in paragraph (e) of this section.

(b) (1) Any manufacturer or other person who holds an approved antibiotic drug file providing for a product that contains saccharin shall sumbit an amendment on or before (9 months after date of publication of final regulation) providing for a revised formulation removing saccharin as an ingredient.

(2) The amendment shall contain:

(i) A full list of articles used as components and a full statement of the composition of the drug product.

(ii) Data showing that the change in composition does not interfere with any assay or other control procedures used in manufacturing the drug product, or that the assay and other control procedures are revised to make them adequate.

(iii) Data to establish that the stability of the product is not adversely affected by the revised formulation. If the data are too limited to support a conclusion that the drug will retain its declared potency for the period allowed by the expiration date, a commitment from the applicant:

(A) To test the stability of marketed batches at reasonable intervals;

(B) To submit the data as they become available; and

(C) To recall from the market any batch found to fall outside the approved specifications for the drug.

(c) No batch of antibiotic drug product containing saccharin as an ingredient will be certified or released after (18 months after date of publication of final regulation).

(d) (1) Any sponsor of a "Notice of Claimed Investigational Exemption for a New Drug" (IND) for a drug product containing saccharin as an ingredient shall amend the IND notice before (9 months after date of publication of final regulation) to provide for a revised formulation removing saccharin as an ingredient.

(2) If the sponsor of an IND notice fails to comply with the provisions of paragraph (d)(1) of this section, the Commissioner will initiate action to terminate the IND notice in accordance with the applicable provisions of section 507 of the act and Parts 312 and 433 of this chapter.

(e) Any person may file a petition in accordance with Part 10 of this chapter to amend paragraph (c) of this section to specify a use of saccharin in a drug product which justifies certification or release of the product. The petition must be supported by the following information:

(1) The amount of saccharin contained in each dose of the drug;

(2) An adequate showing that there are no technically feasible alternatives to the use of saccharin in the drug product, or an adequate showing that the drug product provides a substantial health benefit or other public benefit that would not be available without the use of saccharin; and

(3) A copy of the proposed labeling clearly specifying the saccharin content and its intended use.

PART 510—NEW ANIMAL DRUGS

8. In Part 510, by adding new § 510.414, to read as follows:

§ 510.414 Saccharin.

(a) There are no approved or documented uses of saccharin as an ingredient in animal drugs intended for use in food-producing animals. Information now available demonstrates that saccharin causes malignant bladder tumors in test animals and therefore has a potential for causing cancer in humans. In food-producing animals, the use of saccharin as an ingredient in animal drugs or animal feed requires a demonstration that no residue will be found in food from the edible products derived from those animals, either by an assay designated in accordance with the provisos to the anticancer clauses of the act if it is a carcinogen, or by an assay designated in accordance with the general safety provisions of the act. No such assay has been submitted, nor, to the knowledge of the Commissioner, does such an assay exist. On the basis of this evidence, saccharin has not been shown to be safe for use as an inactive ingredient in animal drugs intended for use in food-producing animals.

(b) Saccharin has been used as an ingredient in some animal drugs intended for use in non-food-producing animals. Saccharin provides no therapeutic benefit to animals and has not been shown to provide any overriding benefit to a measurable animal treatment population. For these reasons, the Commissioner concludes that any risks to animals from the use of saccharin in such drugs outweigh any theoretical benefit alleged from its continued use. Accordingly, on the basis of the new evidence, saccharin has not been shown to be safe for use as an active or inactive ingredient in animal drugs intended for use in non-food-producing animals.

(c) Any drug product that contains saccharin as an inactive ingredient is a new animal drug within the meaning of section 201(w) of the act, and is unlawful and subject to regulatory action under sections 301 and 512 of the act.

(d) Any holder of an approved new animal drug application for a drug product containing saccharin as an inactive ingredient shall submit to the Food and Drug Administration on or before (9 months after date of publication of final regulation) a supplemental application providing for a revised formulation removing saccharin as an ingredient.

(e) If the holder of an approved new animal drug application fails to comply with the provisions of paragraph (d) of this section, the Commissioner will initiate action to withdraw approval of the application in accordance with the applicable provisions of section 512 of the act.

PART 589—SUBSTANCES PROHIBITED FROM USE IN FOOD OR FEED FOR ANIMALS OTHER THAN MAN

9. By adding a new Part 589, consisting at this time of § 589.185, to read as follows:

§ 589.185 Saccharin and its salts.

(a) The food additive saccharin is the chemical, 1,2-benzisothiazolin-3-one-1,1-dioxide ($C_7H_5NO_3S$). Ammonium saccharin, calcium saccharin, and sodium saccharin are produced by the additional neutralization of saccharin with the proper base to yield the desired salt. Saccharin and the named salts have been used as sweetening agents in human food and may have been used as a sweetening agent in food or feed for animals other than man.

(b) Information now available demonstrates that saccharin causes malignant bladder tumors in test animals and therefore has a potential for causing cancer in humans. For this reason it has not been shown to be safe for use in food or feed for animals other than man. In food-producing animals, the use of saccharin as an ingredient in animal feed requires a demonstration that no residue will be found in food from the edible products derived from those animals, either by an assay designated in accordance with the provisos to the anticancer clauses of the act if it is a carcinogen, or by an assay designated in accordance with the general safety provisions of the act. No such assay has been submitted, nor, to the knowledge of the Commissioner, does such an assay exist.

(c) Food or feed for animals other than man containing any added saccharin or saccharin salt is deemed to be adulterated in violation of the act.

PART 700—GENERAL

10. In Part 700, by adding a new § 700.22, to read as follows:

§ 700.22 Use of saccharin as an ingredient in cosmetic products.

(a) Saccharin and its salts have been used as an ingredient in cosmetic products. The ingestion of saccharin has been shown to induce cancer of the bladder in rats. The Commissioner concludes that, on the basis of these findings, saccharin is a deleterious substance that may render injurious to users any cosmetic product that contains saccharin or a saccharin salt as an ingredient and is likely to be ingested under normal conditions of use.

(b) Any cosmetic product containing saccharin or a saccharin salt as an ingredient that is likely to be ingested is deemed to be adulterated and is subject to regulatory action under sections 301 and 601(a) of the Federal Food, Drug, and Cosmetic Act.

Interested persons may, on or before June 14, 1977, submit to the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, Md. 20857, written comments (preferably in quadruplicate and identified with the Hearing Clerk docket number found in brackets in the heading of this document) regarding this proposal. The envelope containing the comment(s) should be prominently marked "SACCHARIN." Received comments may be seen in the above office between the hours of 9 a.m. and 4 p.m., Monday through Friday.

NOTE.—The Food and Drug Administration has determined that this document contains a major proposal requiring preparation of an inflation impact statement under Executive Order 11821 and OMB Circular A-107 and certifies that an inflation impact statement has been prepared. A copy of the inflation impact statement is on file with the Hearing Clerk, Food and Drug Administration.

Dated: April 12, 1977.

DONALD KENNEDY,
Commissioner of Food and Drugs.

[FR Doc.77-11129 Filed 4-14-77;8:45 am]

[21 CFR Parts 145, 150, 172, 180, 189, 310, 430, 510, 589 and 700]

[Doc. No. 77N-0088]

SACCHARIN AND ITS SALTS

Hearing

AGENCY: Food and Drug Administration.

ACTION: Notice of Public Hearing.

SUMMARY: The Commissioner of Food and Drugs announces that a public hearing will be held on May 18 and 19, 1977 to receive information and views from interested persons on the proposed regulations regarding saccharin published elsewhere in this issue of the FEDERAL REGISTER.

DATES: The public hearing will be held on May 18 and 19, 1977 at 9 a.m. A written notice of participation must be filed by May 9, 1977.

ADDRESSES: Written notices of participation should be sent to the Hearing Clerk (HFC-20), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Mr. Ted Herman, Compliance Regulations Policy Staff (HFC-10), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857 (301-443-3480).

SUPPLEMENTARY INFORMATION: Elsewhere in this issue of the FEDERAL REGISTER, the Commissioner is proposing to revoke the interim food additive regulation, 21 CFR 180.37 (formerly 21 CFR 121.4001, prior to recodification published in the FEDERAL REGISTER of March 15, 1977 (42 FR 14302)) under which saccharin and its salts (saccharin) are currently permitted as ingredients in prepackaged food such as soft drinks, and as tabletop nonnutritive sweeteners. The Commissioner is also proposing to accept and promptly review new drug applications for the marketing of saccharin as a single-ingredient drug, available without a physician's prescription. The Commissioner is also proposing to prohibit the use of saccharin in cosmetics that are likely to be ingested, to amend the standards of identity that provide for the use of saccharin, and to prohibit the use of saccharin in animal drugs and animal feed. Comments on the proposal may be submitted until June 14, 1977. Because of the broad public interest in and concern about saccharin, the Commissioner has determined that, in addition to the normal 60-day comment period for receipt of written comments, an informal public hearing should be held regarding the proposal. The purpose of the informal hearing is to provide an open forum for the presentation of information and views concerning all aspects of the proposal by interested persons, be they consumers, scientists, or representatives of manufacturers of regulated products.

In preparing a final regulation, the Commissioner will consider the administrative record of this hearing along with all other written comments received during the comment period specified in the proposal.

The hearing will be held on May 18 and 19, 1977 in the auditorium located on the first floor in the HEW North Building, 330 Independence Ave. SW., Washington, DC 20201. The hearing will begin at 9 a.m. each day. The presiding officer will be Dr. Donald Kennedy, Commissioner of Food and Drugs.

A written notice of participation must be filed pursuant to 21 CFR 12.45 (formerly 21 CFR 2.131 prior to recodification published in the FEDERAL REGISTER of March 22, 1977 (42 FR 15553)) with the Hearing Clerk (HFC-20), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857 not later than May 9, 1977. The envelope containing the notice of participation should be prominently marked "Saccharin Hearing." The notice of participation itself must contain the Hearing Clerk Docket No. 77N-0066, the name, address, and telephone number of the person desiring to make a statement, along with any business affiliation, a summary of the scope of the presentation, and the approximate amount of time being requested for the presentation. A schedule for the hearing will be mailed to each person who files a notice of participation; the schedule will also be available from the FDA Hearing Clerk. Individuals and organizations with common interests are urged to consolidate or coordinate their presentations.

In the event that the responses to this notice of hearing are so numerous that insufficient time is available to accommodate the full amount of time requested in the notices of participation received, the Commissioner will allocate the available time among the persons making the oral presentation to be used as they wish. Formal written statements (preferably in quadruplicate) may be presented to the presiding officer on May 18 and 19 for inclusion in the administrative record.

The hearing will be open to the public. Any interested person who files a written notice of participation may be heard with respect to matters relevant to the issues under consideration.

Dated: April 12, 1977.

DONALD KENNEDY,
Commissioner of Food and Drugs.

[FR Doc.77-11128 Filed 4-14-77;8:45 am]

APPENDIX B

FDA USE OF THE DELANEY CLAUSE

Richard A. Merrill[*]

Set forth below is a brief review of actions by the Food and Drug Administration between 1950 and 1977 to remove substances from the food supply based upon a finding or suspicion of carcinogenicity. This review helps illustrate how the various food safety provisions of the Act have been administered and demonstrates that the Delaney clause has been invoked by FDA infrequently. It should be noted that few of these actions were even contested in the courts, and therefore in some instances the agency was not challenged to clarify the specific legal grounds for its decision.

1. Dulcin and P-4000: In January 1950, prior to the enactment of the original Delaney clause, FDA announced that two artificial sweeteners thought to be carcinogens, dulcin and P-4000 were regarded as "poisonous substances which have no place in any food."[1]

2. Coumarin: In March 1954, FDA announced that any food containing coumarin added as such, or as a constituent of tonka beans or tonka extract, would be regarded as adulterated on the ground that it contained an added poisonous or deleterious substance in violation of section 402(a)(1) of the Act.[2] This action, too, was based upon a finding that coumarin is carcinogenic.

3. DES in poultry: In December 1959, FDA concluded, on the basis of findings of residues in poultry, that the new drug applications (NDAS) for this use of diethylstilbestrol (DES) should be withdrawn. This action was taken under the provisions of section 505(e) of the Act which, prior to 1962, required the agency to demon-

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[*] Prepared for the committee by Richard A. Merrill, Daniel Caplin Professor of Law, University of Virginia, Charlottesville. Professor Merrill was formerly Chief Counsel to the Food and Drug Administration.

strate that the use of the drug was unsafe. The withdrawal of the use of DES in poultry was based on a finding, upheld in the courts, that such use was unsafe:

> On the basis of animal tests and clinical experience, experts have concluded that DES is carcinogen to man. Prolonged exposure to small amounts of carcinogenic substances has been shown to be more dangerous than single or short term exposure to the same or larger quantities. There is no known threshold or safe level for DES, either as a cause or a stimulator of cancer and there is no known methodology by which such a level can be established.[3]

4 Safrole: In December 1960, FDA refused to authorize the use of safrole, oil of sassafras, dihydrosafrole, and iso-safrole in food under the transitional provisions of the Food Additives Amendment.[4] The agency's Federal Register notice also stated that any prior sanction for use of these substances in food was withdrawn. The agency acted on the basis of a determination that safrole is a carcinogen. Since the anti-cancer clause was not formally applicable either to the transitional provisions of the Food Additives Amendment or to substances subject to a prior sanction, this action was based on the general safety provisions of the Act.

5. Flectol H: In April 1967, FDA formally invoked the Delaney clause of the Food Additives Amendment for the first time. On the basis of a determination that it induced cancer when ingested by test animals, the Agency revoked the food additive regulation for 1, 2-dihydro-2, 2, 4-trimethylquinoline, polymerized (Flectol H).[5] This additive had previously been approved for use as a component of food packaging adhesives.

6. Oil of Calamus: In May 1968, FDA announced that, based on a finding of carcinogenicity, oil of calamus could no longer be used as a food flavoring agent.[6] Because use of oil of calamus in food had been based on the determination that it was GRAS--and thus not a food additive--the Delaney clause was not technically applicable. The action therefore can be considered to have been based on section 402(a)(1) of the Act.

7. Cyclamate: In October 1969, FDA similarly announced that, on the basis of a finding of carcinogenicity, cyclamic acid and its salts could no longer be used as a sweetener in food.[7] Because cyclamates had been used on the basis of a determination by the Agency that they were GRAS, this action, too, was taken under the general safety provisions of the Act.

8. Chroanaline: In December 1969, FDA invoked the Delaney clause for the second time when it announced that the additive, 4,4'-methylenebis (2-chroanaline), had been determined to be a carcinogen. It had previously been approved by a food additive regulation for use as a polyurethane curing agent and as a component of food packaging adhesive and polyurethane resins.

9. DES in cattle and sheep: In 1972 and 1973 FDA withdrew approval of the new animal drug applications for use of DES in cattle and sheep. Because the residues being detected in edible tissue were not found by the official methods approved by the agency, the Delaney clause was inapplicable. This action was therefore taken on the ground that, under section 512(e) of the Act, DES was no longer

proved to be safe for these uses. A court subsequently reversed this action on the procedural ground that FDA was obligated to hold an evidentiary hearing before final action could be taken.[8]

10. Diethylpyrocarbonate: In August 1972, FDA withdrew approval of the food additive diethylpyrocarbonate (DEPC) for use in beverages, on the ground that it had been shown to be theoretically capable of combining with other ingredients in beverages to form urethan, a proven carcinogen.[9] Because this reaction was only a possibility, the Agency's action was based on the ground that the additive could no longer be regarded as having been shown to be safe rather than on the Delaney clause.

11. Mercaptins: In November 1973, FDA withdrew approval of the food additive mercaptolmidazoline on the ground that it was possible for the additive to rearrange to form ethylenethiourea, a known carcinogen.[10] This additive had previously been approved for use in the production of vulcanized natural or synthetic rubber closure sealing gaskets and as an accelerator in the production of rubber articles for use in contact with food. Because the feared reaction represented only a possibility, the agency's action was based on the ground that the additive could no longer be regarded as having been shown to be safe, and not on the Delaney clause.

12. Violet No. 1: In April 1973, FDA terminated the provisional listing of the color FD&C Violet No. 1, on the basis of unpublished data from two rat studies suggesting the material may be carcinogenic.[11]

Because this color was only provisionally listed rather than permanently listed, the Delaney clause was technically inapplicable and the action was taken under safety provisions of the transitional provisions of the Color Additive Amendments.

13. FD&C Red No. 2: In February 1976, FDA terminated the provisional listing and certification of FD&C Red No. 2 on the basis of, among other grounds, its apparent carcinogenicity.[12] Again, because the color was only provisionally listed, the Delaney clause did not formally apply, and the action was taken under the safety requirements of the transitional provisions of the Color Additive Amendments.

Other compounds: In addition to the completed product withdrawal actions listed above, FDA has initiated proceedings to remove several other substances from the food supply or to restrict their use, based on a finding or suspicion of carcinogenicity. These substances include chloroform,[13] DES,[14] nitrofurans,[15] polyvinyl chloride in contact with food,[16] acrylonitrile copolymers used to fabricate beverage containers,[17,18] Orange B,[19] and, of course, saccharin.[20] In all of these recent actions the agency has referred to, or relied on, the Delaney clause, except in the action involving polyvinyl chloride.

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References

1. 15 Fed. Reg. 321 (January 19, 1950).

2. 19 Fed. Reg. 1239 (March 5, 1954).

3. Bell v. Goddard, 366 F.2d 177 (7th Cir. 1966).

4. 25 Fed. Reg. 12412 (December 3, 1960).

5. 32 Fed. Reg. 5675 (April 7, 1967).

6. 33 Fed. Reg. 6967 (May 9, 1968).

7. 34 Fed. Reg. 17063 (October 21, 1969).

8. Hess & Clark v. FDA, 495 F.2d 975 (D.C. Cir. 1974).

9. 37 Fed. Reg. 3060 (February 11, 1972); 37 Fed. Reg. 15426 (August 2, 1972).

10. 38 Fed. Reg. 10116 (April 24, 1973); 38 Fed. Reg. 33072 (November 30, 1973).

11. 38 Fed. Reg. 9077 (April 10, 1973).

12. 41 Fed. Reg. 5823 (February 10, 1976).

13. 41 Fed. Reg. 15029 (April 9, 1976).

14. 41 Fed. Reg. 1804 (January 12, 1976); 41 Fed. Reg. 52105 (November 2, 1976).

15. 41 Fed. Reg. 19907 (May 13, 1976).

16. 40 Fed. Reg. 40529 (September 3, 1975).

17. 42 Fed. Reg. 13546 (March 11, 1977).

18. 42 Fed. Reg. 42528 (September 23, 1977).

19. 43 Fed. Reg. 434561 (October 3, 1978, corrected December 5, 1978).

20. 42 Fed. Reg. 19996 (April 15, 1977).

APPENDIX BB

REGULATING CARCINOGENS IN FOOD: A LEGISLATOR'S GUIDE TO THE FOOD SAFETY PROVISIONS OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT

Richard A. Merrill*

I. Introduction

On March 9, 1977, the Food and Drug Administration (FDA) announced that a study in laboratory rats conducted by the Canadian government confirmed that saccharin is an animal carcinogen.[1-A] This finding, the agency stated, required that the sweetener be banned as an ingredient in human food.

FDA's announcement triggered both public incredulity and Congressional demands for revision of the nation's legal framework for regulating food safety. Critics of the agency's action focused on the much-publicized Delaney Clause of the Federal Food, Drug, and Cosmetic Act.[1B] They characterized this provision, which forbids the approval of any "food additive" that is shown to induce cancer in man or in animals,[1-C] as outdated and several ridiculed the test methods employed to evaluate the safety of food ingredients.[1-D] Reacting to these criticisms and to the apparent public indignation over the imminent abolition of the only non-nutritive sweetener approved for use in foods in this country, Congress in late 1977 enacted the Saccharin Study and Labeling Act.[1-E] This legislation forbade any action by FDA against saccharin for 18 months and directed the Secretary of Health, Education and Welfare to arrange for separate studies of the safety and benefits of saccharin and of the current laws regulating food safety. The latter study and a major part of the former were subsequently undertaken by the Institute of Medicine of the National Academy of Sciences.

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* A revised version of this paper is being published as an article in a forthcoming issue of the Michigan Law Review.

The studies mandated by the Saccharin Study and Labeling Act, which are to be reported to Congress, accompanied by the recommendations of the Secretary of HEW,[2-A] should generate a fundamental reexamination of the nation's current food safety policies. A prerequisite for any such inquiry is an understanding of the requirements of the present law. This article seeks to provide this background. The article describes the several statutory provisions that govern the regulation of food constituents and analyzes FDA's implementation of them. Its primary objective is to provide a common starting place for discussion of the contours of future policy. A subsequent article will examine in detail various approaches to regulate risks posed by food, and outline specific recommendations for reform of the present law.

Readers should be advised that the article starts from, and seeks to demonstrate, the premise that many features of the present law are outdated and require revision. In that sense, it may not be an objective treatment. I have conscientiously attempted, however, to reserve judgment about the proper directions of future policy, and to assure that the description and analysis are historically accurate.

A continuing refrain in the furor over saccharin was the claim that the law dictates overreaction to some trivial risks while allowing much graver hazards -- cigarette smoking is the recurrent usual example -- to remain uncontrolled. The central theme of this article is that the current law governing food safety is an aggregation of statutory provisions that represent a patchwork of divergent, sometimes carefully considered but often offhand, legislative policies which invite inconsistent treatment of comparable risks. The Delaney Clause is illustrative of this general characteristic, not because it produces unpredictable results, but because it applies inconsistently, often without regard to the actual risks posed or the benefits provided by various classes of food constituents. The clause's draconian impact magnifies the practical significance of the increasingly irrational distinctions among categories of food constituents that the law now recognizes.[3-AA] These distinctions are the product of the sedimentary process by which the current law, the Federal Food, Drug, and Cosmetic Act, has been created. Beginning in 1906,[3-A] Congress has on a half dozen occasions conferred authority on FDA (or its predecessors) to deal with specified categories of food hazards -- one time addressing first pesticide residues, then food additives generally, later color additives, and finally drugs used in the production of food animals.[3-B] Typically, Congress has added new provisions without replacing, and often without modifying, those already in the law. Furthermore, it has usually failed to explain how the new standards are to mesh with the old.

While the importance of historical context in explaining the enactment and implementation of several provisions in the Act might argue for a chronological treatment, the practical implications of the Act's disparate treatment of different classes of food constituents can best be understood in terms of the categories that comprise FDA's jurisdiction. The legislator considering what sort of food safety legislation should be enacted is probably more interested in knowing how the law now operates than in how it came to be. Accordingly, the body of the article generally follows legal categories in describing how the Act and FDA address food safety. Most of these categories are defined in terms of the origin of constituents, i.e., how they become part of food.

The body of the article, comprising Part III, is an analysis of the legal standards applicable to these several categories of food constituents. Before commencing this analysis, however, the article, in Part II, provides an overview of the food safety provisions of the Act. It then discusses the origin and interpretation of the Delaney Clause, the provision that triggered FDA's action against saccharin and that symbolizes the current debate over food safety policy.

II. Statutory Overview

A. The Food Safety Provisions of the Act

1. The 1938 Act and Its Precedessor. The first federal statute governing food safety, the Food and Drugs Act of 1906,[4a-A] declared to be adulterated any food that contained "any added poisonous or other added deleterious ingredient which may render such article injurious to health."_/ The law did not address hazards posed by constituents other than those "added" to food. Cases brought to enforce this prohibition dealt exclusively with substances purposely incorporated in food or intentionally applied during processing. Although the 1906 Act did not define the term, it established the dichotomy between "added" substances and other constituents of food which permeates the current law's approach to food safety.

When Congress rewrote federal food and drug law in 1938, it sought to expand the 1906 Act's controls over toxicants in food. Initially, the proposed legislation omitted the qualification that a substance be "added." Section 402(a)(1) of the Act[4a-B] declares adulterated any food that "bears or contains any poisonous or deleterious substance which may render it injurious to health. . . ." Almost as an afterthought, Congress modified this standard so far as it applied to food constituents that are not "added." The concluding language of section 402(a)(1) reads: "[B]ut in case the substance is not an added substance such food shall not be considered adulterated under this clause if the quantity of such substance in such food does not ordinarily render it injurious to health," which was intended to be a more difficult standard for FDA to meet.[4a-C] Congress than revived the distinction between substances that are "added" and those that are not, but again failed to define the term "added."

The legal standard applicable to non-added poisonous substances has remained unchanged since 1938. The "ordinarily injurious" test -- only rarely interpreted by the courts -- remains the legal measure of whether a toxicant that occurs naturally in foods, e.g., nitrites in spinach, adulterates the food. Congress has, however, made several changes in the law applicable to "added" constituents of food. As specific categories of "added" food constituents demanded attention, Congress enacted special provisions designed to enable FDA to regulate them more effectively. These provisions have generally authorized FDA to license the use or the occurrence of a class of constituents and flatly prohibited any constituent that the agency has not approved.

In the 1938 Act itself, Congress recognized that certain "added" toxicants in foods required special treatment. In what is now section 402(a)(2)(A), Congress provided that a food containing any amount of an added poisonous or deleterious substance is adulterated -- without imposing on FDA any further obligation to prove a hazard to health. And in section 406,[4b] it empowered FDA to establish tolerances for "added" toxicants whose occurrence in food can not be avoided or whose use is "necessary" to produce the food. In substance, Congress thus authorized FDA to "license" the use of some potentially toxic substances in food, apparently in recognition of their utility or the inability of current production methods to eliminate them. While the legislative history of section 406 is skimpy, Congress' primary objective apparently was to permit continued use of pesticides on raw agricultural commodities, but give FDA an effective means of control by declaring illegal food that contained any quantity in excess of the agency's tolerance.

With the passage of the 1938 Act, therefore, federal law contained three standards applicable to toxicants in foods: (1) section 402(a)(1)'s "ordinarily injurious" standard applied to constituents that fell outside the category of "added"; (2) section 402(a)(1)'s "may render injurious" test applied to "added" constituents that were neither necessary or unavoidable in food production; and (3) "added" constituents whose use was "necessary in the production of a food" or whose occurrence was "unavoidable by good manufacturing practice" were eligible for tolerance setting under section 406. However, Congress did not clarify the distinction between "added" and other constituents, nor did it more precisely define the concepts of "necessary" or "unavoidable" in section 406.

2. Post-1938 Amendments to the Act. This original triad of legal controls has been rendered significantly more complex by subsequent amendments to the 1938 Act. Each of these amendments deals with a sub category of the broad class of "added" food constituents and establishes a system under which FDA is empowered administratively to limit the use, or in the case of pesticide residues the occurrence, of potentially toxic substances in or on food. To further complicate matters, Congress did not establish the same, and perhaps not even consistent, criteria for the exercise of FDA's licensure or tolerance setting authority, a subject that is explored in depth in Part III.

The first of these amendments was the Pesticide Residues Amendment of 1954, now section 408 of the Act.[4-A] This provision was intended to complement the authority then residing in the

Department of Agriculture to register pesticides for use in the United States. The amendment provides, in substance, that a raw agricultural commodity shall be deemed adulterated if it bears any residue of a pesticide that does not conform to a tolerance established under section 408, 4c-B/ and establishes an elaborate procedure by which FDA, and more recently EPA, may establish such a tolerance. 4c-C/

Four years after the passage of the Pesticide Residue Amendments, in 1958, Congress carved out another category of "added" constituents of food for special treatment. The Food Additives Amendment, esstablishes a licensure scheme, similar in basic concept to section 408, for substances intended to be used as ingredients in formulated foods. The Amendment also applies to substances that, through use in food contact articles such as packaging materials, become or "can reasonably be expected to become" components of food. 4c-[illegible]/ A food that bears or contains a food additive whose use FDA has not approved in a food additive regulation, or that contains an approved food additive in a quantity exceeding limits specified by FDA, is adulterated under section 402(a)(2)(C) of the Act. 4c-D

The Food Additives Amendment does not apply to all intentional added ingredients in food or to all substances that may migrate to food. The two most important exceptions to its coverage are substances whose use in food is "generally recognized as safe by qualified experts" (GRAS) -- an exception that embraces a large number of substances, such as sugar and salt. Second, the statutory definition of "food additive" 4c-[illegible]/ excludes substances that either FDA or USDA sanctioned for use in food prior to 1958. Both of these exceptions are use-specific: the status of a substance depends on whether it is GRAS, or was prior sanctioned, for the specific use in question.

In 1960 Congress addressed the more limited problem of substances used to color foods -- as well as drugs, cosmetics, and medical devices.[4d-A] Substances derived from coal tar dyes and used to color foods had previously been regulated under a "harmless per se" standard,[4d-B] which many colors could not meet, while other food colors had been regulated under the general safety provisions of the Act, notably section 402(a)(1).

Unlike the Food Additive Law, the Color Additive Amendments[4d-D] apply to all substances used for the purpose of imparting color to food. The Color Additive Amendments contain no exceptions for colors that are recognized by experts as safe or that were approved for use prior to 1960. The Amendments require FDA approval, or "listing," for each use of a color (e.g., foods, drugs, ingestible cosmetics). A food that bears or contains a color additive whose use in food has not been approved by FDA, or whose use deviates from the terms specified in any FDA approval, is adulterated under section 402(c) of the Act.

The most recent modification in the 1938 Act that are of concern in this context are the Animal Drug Amendments of 1968. Between 1958 and 1967, drugs administered t food producing animals were regulated under a combination of statutory provisions, section 409 as well as the new drug provisions for drugs administered directly to animals that "could reasonably be expected" to leave residues in edible tissues, and section 402(a) in addition to section 409 for compounds administered in animal feeds.[4d-F] In 1967 Congress sought to simplify the procedure for obtaining the approval of drugs used in food producing animals by prescribing a unified licensure system under section 512 of the Act.[4G] Under this system no animal drug that is likely to leave residues in edible tissue of livestock may be used, nor may food containing such residues be marketed, without prior FDA approval.[4H]

Accordingly, by 1968 Congress had subdivided most of the broad class of "added" constituents of human food into several categories subject to special regulatory requirements. Broadly speaking, it required that individual substances be presented to FDA or, in the case of pesticides, to EPA for prior approval, and in general directed that the responsible agency must find a substance safe for human consumption when used as proposed. However, as will be evident, this general instruction has taken varied forms that have not only contributed to the appearance of inconsistency but have given exaggerated practical significance to the initial classification of a substance.

Furthermore, the four categories of food constituents given special attention by Congress in amendments passed since 1938 do not, in FDA's view of the law, exhaust the class of "added" constituents. At no point, either in 1938 or subsequently, has Congress specifically addressed the problem of environmental contaminants, such as PCBs and mercury, where occurrence in food is unintended and undesired and, to a large degree, uncontrollable. While FDA could have regulated contaminants under the "may render injurious" language of section 402(a)(1) or, indeed, in the case of "natural" contaminants such as aflatoxin, under the "ordinarily injurious" language of section 402(a)(1), neither provision would have given the agency authority to determine administratively what levels of such contaminants should be tolerated. Accordingly, from the early 1970's FDA has classified environmental contaminants as "added poisonous or deleterious substances" whose occurrence can not entirely be avoided in order to bring into play the tolerance-setting authority of section 406. The difficulty of controlling contaminants in food and the broad criteria for regulation prescribed by section 406 have led FDA to permit levels of exposure to constituents in this category that contrast sharply with the agency's approach to intentional ingredients, such as saccharin. A principal source of this discrepant treatment of ostensibly similar hazards is the Delaney Clause, which embodies the law's basic "no risk" policy for intentional food constituents but is absent from section 406 and the pesticide residues provision. It is therefore appropriate at this point to examine the origins and interpretation of that provision.

B. History and Impact of the Delaney Clause

The Delaney Clause is perhaps the most discussed, yet possibly the least used, Federal Food, Drug, and Cosmetic provision of the Act. It was added to the law in 1958 as part of the Food Additives Amendment in which Congress for the first time required premarket testing of most intentional food ingredients.[5-A] Prior to 1958, the Act's controls over the safety of food constituents consisted principally of two proscriptions against the distribution of food that was adulterated under section 402(a)(1) or (2).[5-B] These proscriptions were enforced through court action, usually seizures, instituted by the Department of Justice on recommendation from FDA. The agency lacked power to require manufacturers to conduct safety testing of food constituents,[5-C] and had never formally exercised the authority conferred by original section 406 to prescribe tolerances for potentially toxic chemicals in food.[5-D] The Food Additives Amendment put FDA squarely in the business of licensing food ingredients, requiring the agency to find that any "food additive" was safe for its intended use.[5-E]

The Food Additives Amendment was the product of lengthy Congressional consideration of proposals to regulate chemicals in food, which had been stimulated by hearings chaired by Congressman James Delaney of New York.[5-F] The investigating subcommittee's work led first to the passage in 1954 of the amendment permitting FDA to establish tolerances for pesticide residues on raw agricultural commodities[5-G] addressed mainly to intentional food ingredients. The clause that bears Congressman's Delaney's name was not part of the original legislation introduced in the House[6-A] or passed by the Senate[6-B] but was added as an amendment on the House floor after the Department of HEW, on behalf of FDA, withdrew its objections that the clause was redundant.[6-C]

The Delaney Clause now appears in three provisions of the Act: in the 1958 Food Additives Amendment (now section 409(c)(3)(A))[6-D] in the Color Additive Amendments of 1960 (now section 706(b)(5)(B),[6-E] and in the Animal Drug Amendments of 1968 (now section 512(d)(1)(H)).[6-F] While three versions of the clause differ slightly in language,[6-G] their basis thrust is similar, i.e., to prevent the addition to food of any substance that has been shown to induce cancer in man or in laboratory animals. The language of section 409(c)(3)(A) is exemplary:

> No such regulation [authorizing use of a food additive] shall issue if a fair evaluation of the data before the Secretary--
>
> (A) fails to establish that the proposed use of the food additive, under the conditions of use to be specified in the regulation, will be safe: Provided, That no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal. . . .[6-H]

This language seems unequivocal, and certain consequences of the clause are obvious. It accords the same, that is decisive, weight to evidence that a substance induces cancer in animals. Accordingly, when this article refers to a substance as a carcinogen, or to a finding of carcinogenicity it is assumed, unless otherwise noted, that the characterization is based on one or more experiments in laboratory animals, which have become the dominant, indeed almost the exclusive mode for evaluating the safety of food constituents. In addition, the Delaney Clause allows no room for consideration of dose, i.e., it assumes, as a matter of legal policy, that no level of exposure to an animal carcinogen can be considered safe.__/ However, several important critical terms of the clause are not defined, including terms that are said to permit the exercise of scientific judgment, such as "induce," "cancer," and "tests appropriate for the evaluation of the safety of food additives. . . . "[6-I] Thus, for example, the statute does not indicate whether in evaluating an animal experiment FDA is to aggregate benign and malignant tumors, or whether it is sufficient that exposure to an additive is associated with an increase in tumors, even though the mechanism of carcinogenisis is thought to be the result of some predisposing condition that the additive has simply exacerbated. These re issues about which scientists disagree, and which FDA has refrained from attempting to resolve by rule practices. Debate also often arises over the appropriateness of particular tests conducted to determine whether a food additive does induce cancer in laboratory animals.[7-A] Thus, though the policy of the Delaney Clause is clear, in its application scientific judgment has played, and apparently was intended to play, an important role.

The current debate over the Delaney Clause, however, does not focus on the way in which it has been interpreted but rather on its basic premises and potentially dramatic impact.[7-B] My objective is not to document or to defend the judgments FDA scientists have applied in assessing the carcinogenicity of food additives. For present purposes, it is sufficient to record that the agency exercises flexible judgment, in combining malignant and benign tumors, and is usually not persuaded by attempts to explain an increase in tumors as not being "induced" by the test compound.[7-C] On occasion it has discounted apparent findings of carcinogenicity on the ground that the test procedures were not appropriate.[7-D] It routinely insists that ingredients should be tested in accordance with current scientific standards, but nonetheless must often make decisions on the basis of studies that fall short of this criterion.[7-E] Ordinarily, FDA would reject as inappropriate any test of a food additive conducted by a route of administration other than ingestion.[7-F]

In summary, the Delaney Clause affords FDA room to exercise scientific judgment in determining whether its conditions are met by a particular food additive. But the clause affords the agency no flexibility in determining the ultimate regulatory consequences once its scientists have determined that these conditions are satisfied. A food additive that has been found in an appropriate test to induce cancer in laboratory animals may not be approved for use in food for any purpose, at any level, regardless of any "benefits" that it might provide. And if an approved food additive whose benefits have become widely accepted is later found to induce cancer in animals, FDA must terminate its use.[8-A] Evidence that an additive causes other types of adverse effects, by contrast, does not automatically dictate disapproval if FDA can conclude, under the general standards of the Food Additives Amendment, that the conditions of its use pose no significant risk.

The reader should not conclude from this summary, however, that Congress has unequivocally forbidden the introduction or presence of carcinogens in foods. As the previous section reveals, the FD&C Act represents an amalgam of several different, not always consistent provisions designed to assure that foods do not contain harmful constituents. Some of these provisions accord dispositive weight to a finding of carcinogenicity, i.e., to a finding that a substance has induced cancer in laboratory animals, but others prescribe more general criteria for FDA action that do not differentiate between the induction of cancer and other risks to health and that vary in the degree to which they permit the agency to consider factors offsetting such risks.

The result is a patchwork of regulatory approaches that has produced decisons respecting the use or occurrence of specific food constituents that often appear difficult to reconcile.

Part III examines the standards for regulation applicable to each of the several classes of food constituents recognized by the Act. I have used the term "constituent" to embrace all substances that comprise or become a part of food. The term does not appear in the Act, which, as the reader is now aware, subdivides the universe of food constituents into numerous smaller categories--such as "food additives" or "pesticide residues"--to which special rules apply. Except when the word "constituent" is used in undifferentiated fashion to apply to any or all of these categories, the article employs the terminology established by the Act.

III. Statutory Standards for Regulating Constituents of Human Food

Congress' current food safety "policy" must be distilled from the several overlapping provisions of the FD&C Act that have been enacted at different times during or since 1938. These various provisions focus either on the way in which constituents become part of food, e.g., as residues of pesticides, or on the functions they serve, e.g., color additives, rather than on the risks to human health they present or the benefits they provide. Each provision addresses these elements--if at all--largely without regard to the treatment accorded other classes of food constituents.

For purposes of discussion, constituents of food can be divided into four general categories based upon their source of origin. Some of these categories in turn include subclasses of constituents that are themselves subject to distinctive statutory standards. The following sections describe and analyze FDA's current interpretation of specific statutory provisions, an interpretation that in some instances may be subject to dispute. Where the agency's prevailing position remains untested or differs from an earlier interpretation, this fact is noted and any significant differences are discussed. The four broad categories are:

A. Natural constituents of food, e.g., ascorbic acid in oranges, nitrates in spinach.

B. Environmental contaminants of food, which FDA has characterized as "added" on the theory that they are not inherent even though they may in some measure be unavoidable in some foods, e.g., PCBs in fish, mycotoxins in or on many grains.

C. Substances used intentionally as food ingredients, e.g., salt, saccharin, Red No. 2, sodium nitrite.

D. Substances that become constituents of human food through the intended use for other purposes, which may or may not be food-related, e.g., food packaging materials, animal drugs, and pesticides.

This subdivision breakdown of food constituents into discrete categories is potentially misleading, for some constituents fall into more than one category. Nitrate, for example, occurs naturally in many vegetables and has been used as an intentional added ingredient of some processed meats. Ascorbic acid is a natural constituent of oranges, but may also be added to processed foods to provide Vitamin C. Furthermore, it may sometimes be difficult to determine which category a given constituent of a specific food fits into. DDT residues in fish may now be considered an unavoidable environmental contaminant but their occurrence originally can be attributed to human efforts to control agricultural pests. Before DDT was banned as a pesticide, tolerances had been established for DDT residues on agricultural commodities in accordance with section 408 of the Act, and some tolerances remain in effect because DDT's persistence in the environment makes its presence in some foods unavoidable.

The following sections outline the current statutory criteria applicable to each of the foregoing categories of food constituents, and briefly describe the varied legal processes by which these criteria are applied. In each instance specific attention is given to the regulatory significance to be accorded a finding that a constituent induces cancer in experimental animals.

A. Natural Food Constituents

Section 402(a)(1) of the Act[11-A] sets forth[11-AA] the safety standard applicable to naturally occurring food constituents. Under this provision a food is deemed to be adulterated

> it if bears or contains any poisonous or deleterious substance which may render it injurious to health; but in case the substance is not an added substance such food shall not be considered adulterated under this clause if the quantity of such substance in such food does not ordinarily render it injurious to health. . . . [11-B]

The legislative history of the 1938 Act, where this languge first appeared, provides little guidance as to how it is to be interpreted.[11-C] Congress evidently was aware that some foods naturally contain substances that, if consumed in excess, can be harmful, and quite clearly it intended to establish a demanding standard for FDA enforcement. The provision makes no specific mention of the risk of cancer, and not surprisingly, there is no evidence Congress anticipated that a natural food might itself cause cancer or--a more common occurrence--be found naturally to contain a substance that induces cancer when fed to laboratory animals.

Judicial construction of the "ordinarily injurious" standard is surprisingly sparse. However, the few cases, as well as the legislative history, indicate that FDA must be able to show that the amount of a naturally occurring poisonous substance is sufficient to render the food in which it occurs injurious when consumed in ordinary quantities by ordinary consumers. The leading case, *United States v. 1232 Cases of American Beauty Brand Oysters*,[12-A] involved an FDA seizure of oysters that contained shell fragments which the government claimed were capable of becoming lodged in the esophagus or injuring the mouth. The court observed that section 402(a)(1) contemplates that "there may be of necessity food products containing deleterious substances."[12-B] It found that the shell fragments could not be entirely removed, even though the claimant employed the most modern processing techniques, and that the quantity of fragments did not exceed that in the products of other processors. The court was also moved by the claimant's showing that it had distributed over 50 million cans without receiving any complaints about the presence of shell fragments. Accordingly, it concluded, the oysters had not been shown to be dangerous in ordinary use:

> . . . [Because] it is impossible to eliminate shell fragments in toto from the product, the use of oysters as a food must be entirely prohibited or it must be found that the presence of shell fragments is not a deleterious substance within the meaning of the law and must be tolerated. To reject oyster products as a food is unthinkable. It would be as reasonable to reject fish because of the presence of bones.[12-C]

The court's statement assumes that notwithstanding the risk of choking or other injury from oyster shell fragments, Congress would regard oysters as sufficiently important to preclude a finding of adulteration. While the Act does not explicitly authorize such a rough weighing of benefits, the court's approach is consistent with the few illustrations contained in the legislative history of section 401(a)(1). The bill's proponents clearly did not want to ban coffee, although they acknowledged that excessive consumption of caffeine could be injurious to health. Their desire to control the marketing of mushrooms and mussels but not rhubarb suggests that the "ordinarily injurious" standard was meant to permit FDA, or a district court, to weigh the relative dangers and importance of foods that naturally contain poisonous constituents.[12-A]

This does not mean that FDA could not restrict the marketing of a food that naturally contained a constituent shown to be an animal carcinogen. In the state of current scientific knowledge, the agency could contend that any quantity of a carcinogen poses a hazard for at least a small number of consumers. However, FDA has never applied this premise to a natural constituent of food. The sparse case law would suggest that the agency would have to demonstrate a probability of harm to some significant number of consumers. Thus, section 402(a)(1) would appear to allow, and perhaps require, FDA to consider whether a naturally occurring carcinogen is present in amounts sufficient to present a serious risk. And the agency has assumed without ever explicitly so stating, that under 402(a)(1) its assessment of the seriousness of such a risk may legitimately embrace some evaluation of the "benefits" of the food itself.

Section 402(a)(1) is enforced primarily through seizure or other court action. The Act does not require the distributor of a commodity to seek approval of the safety of its natural constituents, nor does it provide a procedure for administratively withdrawing permission to market a food that naturally contains an unsafe constituent. Theoretically, FDA could promulgate a regulation declaring that a particular natural constituent is an adulterant--and approach it has taken with some added food constituents which had never been "licensed."[13-B] But even in such a case the agency would have to enforce its determination through judicial action, and it is unclear what weight a court would accord in such a suit to the agency's determination. FDA bears the burden of initiating any action to challenge the safety of a natural constituent of food. Accordingly, its determination that a natural constituent is not present in amounts sufficient to cause harm, or that the importance of the food outweighs any risk, is reflected simply in court inaction, and is therefore likely to be beyond effective review.[14-A] The Act does not impose, and FDA has not assumed, any responsibility to announce or document such decisions administratively.

B. "Unavoidable," "Added" Constituents of Food

An important and increasingly numerous group of food constituents are those that, although not inherent in agricultural commodities, unintentionally contaminate foods such as grains, vegetables, meat, milk, and fish during harvesting or production. Such environmental contaminants are common; they include aflatoxin on peanuts and grains, polychlorinated biphenyls (PCBs) in fish and milk, and mercury in swordfish and other marine species. Most such contaminants are considered "poisonous or deleterious," because they are capable of producing toxic effects at some level of exposure. Some, such as PCBs, have been shown to be carcinogenic in test animals. Aflatoxins are acknowledged animal carcinogens and strongly suspected of causing human cancers as well.

FDA characterizes these and other environmental contaminants as "unavoidable,"[15-A] but this term is used in a special sense. A person who desires to eat swordfish cannot avoid finite quantities of mercury, which apparently contaminates all of the species. But one could "avoid" mercury by not eating swordfish (or other foods) that are contaminated by the substance.[15-B] FDA's characterization thus initially assumes the desirability or value, of foods containing environmental contaminants, and focuses on the ability of manufacturers and processers to eliminate the contamination. Under the agency's interpretation, the degree to which such a contaminant may be "avoided" depends not only on the levels at which it occurs but on the practicability of the various methods by which contaminated food can be prepared for distribution or consumption.[15-CC]

While FDA's interpretation of the "unavoidability" criterion of section 406 may be entirely consonant with Congressional expectation, it is appropriate to contrast its apporach to environmental contaminants with the law's treatment of direct food additives. FDA has prudently concluded that Congress would not expect it to ban the distribution of peanuts in order to prevent human exposure to aflatoxins, but the Food Additive provisions make no allowance for the fact that, in current circumstances, saccharin is an essential, an unavoidable ingredient of low calorie soft drinks. The banning of saccharin will effectively prevent the marketing of such products altogether. Similarly, saccharin can be viewed as at least as indispensable in the production of low calorie soft drinks as pesticides are in the production of most agricultural commodities, the very circumstance for which Congress devised section 406.

This analysis is not simply a linguistic game. The classification of PCBs, for example, as an unavoidable environmental contaminant permits FDA to avoid the Strictures of the Delaney Clause. The agency has concluded that the Delaney Clause does not apply to such "unavoidable" food contaminants, for two reasons.[15-C] First, although it considers environmental contaminants to be "added" substances within the meaning of the first clause of section 402(a)(1),[15-D] it acknowledges that they could not be approved as "food additives" because they serve no functional purpose in food. A food additive must be capable of accomplishing an intended technical effect before it can be approved.[16-A] Second, FDA has assumed that Congress did not intend section 409 to reach constituents whose addition to, or presence in, food cannot be fully controlled by human intervention. The Food Additives Amendment was designed to regulate ingredients used to make food and constituents, such as packaging materials, that became part of food through intentional use for other purposes.[16-B] FDA has therefore regulated "unavoidable" food contaminants under other provisions of the Act, either section 402(a)(1) or section 402(a)(2) plus section 406. As the following discussion indicates, the interrelation of these three provisions, enacted simultaneously in 1938, poses difficult problems of interpretation. FDA's current construction represents an attempt to distill a unified policy out of language that defies consistent interpretation.[16-C]

1. Section 402(a)(1). As observed in Part II, section 402 (a)(1) applies a more rigorous standard to "added" contaminants of food than to naturally occurring poisons. The full statutory language provides that a food is adulterated "if it bears or contains any poisonous or deleterious substance which may render it injurious to health. . . ."[17-A] The addition, in the next sentence, of the "ordinarily injurious" standard addressed specifically to naturally occurring deleterious substances makes inescapable the inference that this initial clause applies to "added toxicants."[17-B]

The "may render injurious" standard was carried over from the 1906 Act.[17-C] The authoritative interpretation of this phrase is still the Supreme Court's opinion in United States v. Lexington Mill and Elevator Co., a case decided under the older law.[17-D] In Lexington Mill, FDA sought to condemn flour which had been treated with nitrogen peroxide gas, small quantities of which remained on the food. The Supreme Court affirmed a lower court ruling that the jury had been erroneously instructed that the addition of a poisonous substance in any quantity would render food adulterated. In its opinion the Court made clear that the "may render" standard applied not to the added constituent, but to the food that contains it, which the Government had the burden of showing "may be injurious" to consumers. The Court also made clear, however, that the FDA need not prove conclusively that a food containing an added poison would cause injury for it to be condemned. The "may render" test would be satisfied if it demonstrated any significant possibility that the food would be injurious. Consideration could be given to the various ways in which the food might be used and to the vulnerability of individuals to whom it might be fed, e.g., the sick, the young, the aged, etc.). If food, because of an added substance, "may possibly injure the health of any of these," the statute is satisfied. "If, on the other hand, it cannot by any possibility, when the facts are reasonably considered, injure the health of any consumer, such [food], though having a small addition of poisonous or deleterious ingredients, may not be condemned under the act."[18-A]

Congress consciously sought to carry over this interperetation when it incorporated the first clause of Section 402(2)(1) in the 1938 Act.[18-AB] The key issue under the "may render injurious" standard is the quantity of the added substance in the food. In United States v. Commonwealth Brewing Corp., et al.,[18-B] the court acknowledged that in toxicology quantity is important in determining whether or not a deleterious substance may be harmful and therefore concluded that "quantity would be the test under [§ 402(a)-(1)]."[18-C] This element would appear to be an essential inquiry under the "ordinary injurious" standard as well. The chief distinctions between the two adulteration standards in section 402(a)(1) appear to be the greater of probability of harm that the government must show to restrict a natural constituent and its ability, under the "may render" standard, to take account of specially vulnerable segments of the population. Under either standard the Government must prove that the food itself probably will, or may, injure health, and not merely that it contains a poisonous substance. If the substance is not added, it must be present in such quantities that the food is likely to be injurious under ordinary conditions of use. If any likely use of a food containing an added toxicant would pose a risk of harm, the food is adulterated.

Because the statute imposes a more rigorous standard on "added" substances, FDA has historically espoused a broad interpretation of the term "added." In regulations published in final form in 1977, the agency affirmed its position that any substance, including natural environmental contaminants such as mercury, that is not an "inherent" constituent of a food is subject to regulation as an "added" substance.[19-A] Any substance incorporated in or added to a food, or used intentionally in proximity to food in a fashion that results in migration, would obvioulsy also fall in this category. Furthermore, FDA asserts, if the quantity that would naturally be present, e.g., because of absorption from the environment, the excess is an "added" substance under section 402(a)(1).[19-B] In short, in the agency's view, the first clause of section 402(a)(1) applies to the great majority of deleterious substances that may occur in human food.

It should be emphasized that the first clause of section 402(a)(1), just as the clause applicalbe to naturally occurring adulterants, is a prohibitory standard, not a licensing provision. To enforce section 402(a)(1), FDA ordinarily must locate contaminated food, conduct chemical analyses, find witnesses prepared to testify that the amount of the contaminant is potentially harmful to someportion of consumers, and prove these facts in court. By itself, the provision gives the agency no authority to evaluate or approve the safety of a substance before it is "added" to food.[19-C]

2. Section 402(a)(2)(A) and 406. The two clauses of section 402(a)(1) would theoretically have provided a comprehensive, though concededly ineffective, framework for regulating food safety. Together they cover all substances that may render food unsafe, both indigenous and added, but they are inadequate in two important respects. First, neither clause authrizes FDA to assess the safety of a constituent or of a food before consumers are exposed. Enforcement of both standards is after the fact. A second problem with section 402(a)(1)'s "may render injurious" standard is that it does not appear to allow consideration of the possible benefits of an added substance, or of the costs of removing from food a substance whose occurrence is largely beyond the capability of producers to control.

Although the legislative history is not fully illuminating, Congress obviously was sensitive to this second difficulty when it enacted the 1938 Act. It included two other provisions that were designed to permit FDA to establish tolerances for added poisonour or deleterious substances that provide some benefit--either because they cannot be avoided in some foods that are considered to be important or because their use contributes significantly to food production.

Section 402(a)(2)(A) of the Act specifies that a food shall be deemed adulterated

> if it bears or contains any added poisonour or added deleterious substance . . . which is unsafe within the meaning of section 406 . . .[20-A]

And section 406 provides:

> Any poisonous or deleterious substance added to any food, except where such substance is required in the production thereof or cannot be avoided by good manufacturing practice shall be deemed to be unsafe for purposes of the application of clause (2)(A) of section 402(a); but when such substance

> is so required or cannot be avoided, the Secretary shall promulgate regulations limiting the quantity therein or thereon to such extent as he finds necessary for the protection of public health, and any quantity exceeding the limits so fixed shall also be deemed to be unsafe for purposes of the application of clause (2)(A) of section 402(a). . . . In determining the quantity of such added substance to be tolerated in or on different articles of food the Secretary shall take into account the extent to which the use of such substance is required or cannot be avoided in the production of each such article, and the other ways in which the consumer may be affected by the same or other poisonous or deleterious substances.[20-B]

This language satisfies the requirements of section 402(a)(2), but it does not cure the problem posed by section 402(a)(1)'s prohibition of any "added" poisonous substance that "may render" food injurious to consumers. Congress therefore added the following additional caveat to section 406:

> While such a regulation is in effect limiting the quantity of any such substance in the case of any food, such food shall not, by reason of bearing or containing any added amount of such substance, be considered to be adulterated within the meaning of clause (1) of section 402(a).[21-A]

As with may other provisions of the 1938 Act, the legislative history of section 406 provides only suggestive guidance respecting the sorts of "added" toxicants Congress expected FDA to set tolerances for.[21-B] Pesticides were obviously the primary candidates for the establishment of tolerances. It is questionable whether Congress visualized that FDA might, as it has done, use section 406 to control environmental contaminants without flatly proscribing the marketing of contaminated foods under section 402(a)(1).[21-C] The point is somewhat academic, for FDA never attempted to exercise its authority to establish formal tolerances for any "added" poison until well into the 1970's. The agency attempted to control pesticide residues on raw commodities through informal administrative tolerances--levels that would cause it to initiate regulatory action under section 402(a)(1).[21-D] These administrative tolerances were apparently known to producers and distributors of foods but were never published, much less made the subject of public rulemaking.[21-E]

In 1954 Congress enacted section 408 of the Act, which explicitly empowered FDA to establish tolerances for pesticide residues on raw agricultural commodities.[21-F] With this amendment, section 406 lost importance[21-G] until recognition of widespread environmental contamination of basic foods by compounds such as PCBs, mercury, and various mycotoxins convinced FDA that it needed a statutory mechanism to control consumer exposure.[21-H] Since the early 1970's, section 406 has provided the legal framework within which FDA has regulated environmental contaminants and other "unavoidable" by-products of modern food production, such as lead in the solder used to seal tin cans.[22-A] It therefore is pertinent to examine the criteria applicable under this provision.

Most notably, section 406, which is enforced through section 402 (a)(2)(A), does not unequivocably preclude the marketing of food that contains an added carcinogenic substance. Indeed, the section does not mention or differentiate among specific risks to health. FDA has taken the position that it may establish a tolerance for a contaminant shown to be carcinogenic--and thus "approve" its presence in food in quantities below the tolerance--if the criteria of section 406 are met.[22-B] To be eligible for 406 tolerance a substance must be one that cannot avoided through good manufacturing practice or that is "necessary in the production" of a food.[22-BB] In establishing a tolerance, the statute specifies that FDA shall consider two criteria: (1) the level whose consumption will not pose a risk to public health, taking into account other ways in which consumers may be exposed to the substance, and (2) the extent to which occurrence of the substance can be reduced through good manufacturing practice.[22-C] If careful processing or storage can achieve lower levels of a contaminant than health considerations might otherwise dictate, the agency presumably is obligated to establish any tolerance at such lower levels.[22-D]

Read literally, section 406 would present FDA with an insoluble dilemma. The section specifies that the agency "shall" establish a tolerance for any added poisonour substance that cannot be eliminated through good manufacturing practice. At the same time it implies that any tolerance may not exceed the level that poses no risk to health. However, the lowest achievable level of some environmental contaminants undoubtedly exceeds the level that can confidently be determined to be safe. For a contaminant, such as aflatoxin, that has been shown to be an unequivocal animal and probable human carcinogen, most scientists would agree that no level of exposure can be judged safe for all individuals. Yet section 406 does not appear to contemplate that, in such a circumstance, forbidding marketing of the contaminated food is an appropriate, or even tenable, option.

FDA has essentially ignored this textual dilemma. The agency has never acknoeledged that it is obligated to establish tolerances for all "unavoidable" contaiminants of food regardless of the risks posed to consumer health. At the same time, it has declined to adopt the "no threshhold" rationale for regulation of carcinogenic contaminants of important food products, most notably peanuts contaminated with aflatoxin. In effect the agency has interpreted section 406 as permitting consideration of the value of the food, as well as the potency of the contaminant and the extent to which its occurrence can be controlled. Such consideration is seldom explicit and usually conducted under the guise of assessing the practicability of various storage or processing procedures designed to reduce or eliminate the substance.

A third criterion, not explicitly sancioned by the Act, is nonetheless considered by FDA in establishing a section 406 tolerance: the capability of analytical methods to measure the contaminant.[22-E] No agency can enforce a tolerance for a substance below the level that practicalbe methods of analysis can detect. The capability of chemical analysis can be a primary determinant of a tolerance for a toxic contaminant if, for example, the best method available is not sufficiently sensitive to measure levels that theoretically are avoidable.[23-A] If no method were capable of measuring the level considered necessary to protect public health, the agency would be faced with having to establish a tolerance at a level it could not enforce. One possible conclusion--that the criteria of section 406 could not be met--would be unenforceable because FDA could not establish a violation of section 402(a)(1) or (2)(A) if it could not find, or prove the presence of, the theoretically "unlawful" contaminant. In such a case, the tolerance selected would be set at the current limit of detection of the best practicable analytical method.

The Act prescribes an elaborate procedure for the establishing of tolerances under section 406, which in part accounts for FDA's failure for many years to make use of this section.[23-B] The agency must first publish a proposed tolerance and invite public comments. After evaluating the comments, the agency must publish a "final order" to which objections can be filed, together with requests for a formal evidentiary hearing. The filing of objections accompanied by an adequate request for a hearing operates to stay FDA's tolerance pending the hearing.[23-C] Following the completion of the formal administrative proceedings, including an administrative law judge's initial decision and any appeal to the Commissioner of Food and Drugs, the agency issues an order establishing the tolerance, which is subject to review in the courts of appeals.[23-D]

Partly because of the expense and duration of the procedure for establishing formal tolerances, FDA has devised an informal system for prescribing "action levels" for environmental contaminants of food.[24-A] An action level specifies the quantity of an added poisonous substance that will cause FDA to initiate court enforcement action against a fraud under section 402(a)(1).[24-B] It represents a formalized exercise of the agency's prosecutorial judgment, although it does not carry the same authoritative weight in enforcement proceedings as a formal 406 tolerance.[24-B] FDA regulations state that it will establish an action level for a contaminant, rather than initiate proceedings to establish a formal tolerance, when data on safe levels of exposure are incomplete or the levels at which the contaminant is occurring appear to be in a state of flux.[24-C] The same criteria ostensibly govern the agency's setting of action levels as apply to its establishment of formal 406 tolerances.

As noted previously, for many years FDA regulated the occurrence of pesticide resideus on raw agricultural commodities through a system of informal administrative tolerances, which served the same function as the current action levels. Because of the current interest in environmental contaminants and the controversiality of judgments about the safety of levels of exposure and about the capability of food manufacturers to reduce them, however,[24-D] FDA now provides an opportunity, albeit limited, for members of the public to participate in its establishment of action levels. When the agency identifies a contaminant that requires control, e.g., kepone in fish, it announces in the FEderal Register the action level at which it will initiate court enforcement. Simultaneously, the agency makes available for public examination whatever toxicity and human exposure data underlie its intiial determination. Interested persons may submit comments on the exposure level approved and the agency may respond to the comments if it is persuaded that the level initially announced should be revised.[24-E] This procedure represents an advance over the agency's older practice, which action levels were not publicly disclosed, but it falls short of providing an effective opportunity for debate over the agency's judgment, respecting safety, avoidability, and value of the food.

C. Intentional Ingredients of Processed Foods

For purposes of legal analysis, this third category of food constituents must be subdivided into four subcategories which, although they present similar problems of safety evaluation and regulatory control, are subject to different statutory treatment. These four subcategories are artificial creations of statute; they do not correspond to functional categories recognized in the production of food. Furthermore, the classifications themselves are farmed in arcane language to capture historical distinctions that bear no relation to either fundamental or safety criteria. The Act's definition of "food additive," set forth below, is illustrative. The four subcategories are: (1) "food additives" used directly in making foods, (2) ingredients that are "generally recognized as safe," (3) "prior sanctioned substances" used as ingredients in food, and (4) "color additives."

Popular misconception assumes "food additives" are artificial substances used in food production while natural ingredients, such as salt or potatoes, are simply that, namely, ingredients. In fact, not every artificial substance used to formulate food is a food additive. Moreover, the Act does not distinguish between ingredients that are produced by chemical synthesis and those produced naturally by agriculture. The definition of food additive, which appears in section 201(s) of the Act,[25-A] embraces both artificial and natural substances and simultaneously excludes several important classes of ingredients:

> The term "food additive" means any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food (including any substance intended for use in producing, manufacturing, packing,

> processing, preparing, treating, packaging, transporting, or holding food; and including any source of radiation intended for any such use), if such substance is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use; except that such term does not include--
>
> * * *
>
> (3) A color additive; or
>
> (4) any substance used in accordance with a sanction or approval granted prior to the enactment of this paragraph . . . pursuant to this Act, the Poultry Products Inspection Act . . . or the Meat Inspection Act of March 4, 1907. . . .[26-A]

The subcategory of food additives thus does not include substances whose use in food is "generally recognized as safe" by qualified experts, a category commonly referred to by the acronym GRAS. In addition, the definition excludes most ingredients that either FDA, or the Department of Agriculture in the case of meat and poultry, had sanctioned for use in food prior to September 6, 1958. It also excludes color additives. Each of these exceptions is examined following a discussion of the requirements applicable to food additives.

1. Direct food additives. Any ingredient that is a food additive, i.e., that is not GRAS, must be the subject of an approved food additive regulation before it may lawfully be used in food.[26-B] FDA may not approve a food additive unless it meets certain basic criteria. Most important, an additive must have been shown to be safe under the conditions of its intended use. This requires a demonstration that, with reasonable certainty, the additive will have no adverse effects on the health of consumers.[26-C] The Delaney Clause reinforces this requirement by flatly prohibiting the approval of a food additive that has been shown to induce cancer in man or, by ingestion or other appropriate tests, in animals.[26-D]

A food additive must also be shown to be functional, i.e., capable of accomplishing its intended technical effect.[26-E] For example, a preservative must preserve when used in the quantities intended. If this elementary criterion is satisfied, however, FDA may not demand any showing of the additive's broader utility, or consider the availability of alternatives that would accomplish the same technical effect.[27-A] The Food Additives Amendment acknowledges the "benefits" many additives can provide, but reflects Congress' judgment that the market--and not the Government--should determine the extent to which "safe" food additives are used.[27-B]

FDA is empowered to prescribe conditions necessary to assure that an additive's use will be safe.[27-C] Such conditions typically include limitations on the levels of use and can also include restrictions on the foods to which it is added or on the purposes for which it may be used. Occasionally, FDA may also prescribe the form in which an additive may be marketed, e.g., solely as a tabletop sweetener.[27-D] And the act explicitly permits the agency to prescribe labeling for the additive, apparently to provide information to commerical users.[27-E] In addition, on occasion, FDA has, thus far without formal legal challenge, prescribed special labeling requirements for the finished foods in which an additive is used.[27-F]

Because section 409 requires FDA to verify the safety of a food additive before it may lawfully be used, the petitioner seeking approval, usually the manufacturer of a potential user, must submit to the agency data sufficient to support such a determination.[27-G] FDA has developed and generally adheres to informal standards for the tosicological tests a petitioner must submit to establish the safety of a food additive.[27-H] The type and extent of testing required are likely to vary with the quantities in which, and the purposes for which, the additive is to be used. Although it has not always done so, FDA reportedly now requires that any direct additive proposed for use at significant levels in food be tested in long-term animal feeding studies to determine whether it may induce cancer other chronic effects. The agency also now requires testing for teratogenic effects (birth defects) and often suggests, though it does not require, mutagenesis testing.[27-I]

While occasionally a petitioner may feed an additive to human volunteers[27-J] --usually to demonstrate palatability of functionality-- the data for evaluating safety are derived almost exclusively from studies in experimental animals. The critical tests are those designed to yield probabilistic answers to broad questions, such as whether an additive causes cancer. If a food additive is found to induce cancer in animal tests, its use may not be approved at any level. If the chronic effects noted do not inlcude cancer, the agency applies a "safety factor" to determine permissible human exposure. Except in special cases,[28-X] the agency adheres to a safety factor of 100, dividing the dose at which no adverse effects are observed in the animals by 100 to arrive at a dose that will, with reasonable certainty, be safe in humans.[28-A] If the agency is prepared to act on the basis of short-term, or acute studies alone, as it does in evaluating many indirect additives to which exposure is lower, it will apply a higher safety factor, usually 1000.

FDA would be the first to acknowledge that this process does not guarantee that an additive may not prove harmful to some individuals. There continues to be debate over whether experimental animals are suitable models for evaluating the likely effects of a substance in humans. A 100-fold safety factor is, in the final analysis arbitrary, justified as much by the ease of use as by any theory of comparative biology.[28-B] And the relatively small numbers of animals typically in feeding studies limit the statistical reliability of a finding that a particular dose produces no adverse effects.[28-C] FDA's determination that an additive is "safe" is therefore vulnerable to several uncertainties. But the licensure process for food additives provides far greater assurance of the reliability of such determinations than can be ascribed to judgments about the safety of other categories of food constituents, such as environmental contaminants, on which little testing may ever have been done and which FDA must take the initiative to control.[28-D]

The statutorily prescribed process for approval or withdrawal of approval of a food additive is on its face as complex as that required for the establishment of tolerances under section 406,[29-A] although the procedures are not identical. FDA is required to announce in the Federal Register the filing of any petition for a food additive regulation--the equivalent of the petitioner's "proposal"--and later publish a final order of approval or disapproval.[29-B] If a petition is accepted for filing, the agency almost always will approve the additive.[29-Ba] Any person who is adversely affected by the agency's action, approving or denying approval, may file objections and request a formal evidentiary hearing.[29-C] Under section 409, however, FDA need not stay its order pending any hearing required on the objections; thus, the agency's approval of an additive may become effective even though it has granted a hearing on its underlying funding of safety.[29-D] The Commission'ers final decision following a hearing is subject to review in a court of appeals.[29-E] Essentially the same procedure must be followed when FDA seeks to terminate use of an approved food additive, even if the agency's basis for withdrawal is that the additive has been shown to induce cancer.[29-F] The Act provides no means for abbreviating this process when a petitioner or other objectors insist on their full procedural rights. However, the elaborate procedure prescribed by statute is rarely followed in full. Most food additive petitions are eventually approved, and in twenty years only two have provoked demands for a formal hearing.[29-X]

2. Ingredients generally recognized as safe (GRAS). As noted above, the statutory definition of "food additive" excludes ingredients that are

> generally recognized, among experts qualified by scientific training and experience to evaluate [their] safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use. . . . [29-G]

Congress limited the coverage of the Food Additives Amendment in this fashion principally so that ingredients which had long been used in foods without evident harmful effect, such as salt, sugar, and other familiar substances, would not have to undergo extensive new testing.[30-A] The GRAS exception may therefore be viewed as a crude Congressional judgment about the proper priority for FDA's evaluation of the safety of food ingredients. It has also occasionally bee in accurately characterized as a "grandfather clause."[30-B]

Numerous cases have construed the basic criteria for GRAS status.[30-C] As the statute itself indicates, there are two classes of GRAS ingredients: (a) ingredients currently recognized by experts as safe based on their common use in food prior to 1958 (usage alone after 1958 cannot support GRAS status for this category),[30-D] and (b) ingredients generally recognized by experts as safe based on the results of toxicological testing, whether such testing was conducted before or after 1958.[30-E] Recognition of an ingredient's safety need not be unanimous among experts, but it must at least be predominant.[30-F] FDA will reject a claim to GRAS status based upon animal test results ("scientific procedures") that have not been published in the scientific literature, where they can be evaluated by the scientific community.[30-G]

The Act does not explicitly allow any consideration of utility of benefit in determining whether an ingredient is GRAS. Thus, the fact that salt possesses important preservative qualities in theory should not enter into a determination of whether it is GRAS. However, even scientists' judgments about the safety of an ingredient that has been used for centuries prior to 1958 are likely to be influenced by their awareness of the ingredient's utility. In this connection, it should be emphasized that the conclusion that an ingredient is not "generally recognized as safe" does not automatically preclude its use. If adequate evidence can be assembled to demonstrate that the ingredient presents no risk to consumers, it may be approved as a food additive under section 409(c).[31-A]

GRAS status is conditioned upon the user's observance of specified restrictions, for many ingregients, including limits on levels, source, purpose, and even on the foods to which an ingredient may be added.[31-B] FDA's published list of selected GRAS ingredients specifies limitations that in many instances are comparable to those imposed on the use of approved food additives.[31-C] However, FDA has only occasionally attempted to prescribe special labeling requirements for a GRAS ingredient or for the foods in which it is used.[31-D]

Because GRAS ingredients do not fall within the definition of "food additive," they are not technically subject to the Delaney Clause. In practice, however the Delaney principle prevents the introduction or continued use of a GRAS ingredient that is found in appropriate tests to induce cancer in experimental animals.[31-E] Such a finding would undermine any basis for general expert recognition of the safety of the ingredient, and thereby render it a food additive for which affirmative FDA approval was required--approval that the Delaney Clause would then formally preclude. This analysis explains FDA's actions in the case of cyclamate, which prior to 1970 had been in wide use based on the belief that it was GRAS.[31-F] A report by the principal manufacturer of cyclamate that the substance might be a test animal carcinogen was viewed as destroying its GRAS status making its continued use unlawful overnight.[31-G]

The cyclamate episode illustrates an important distinction between ingredients that are expected from the food additive definition because they are GRAS and ingredients that are exempt because FDA or USDA had sanctioned their use prior to 1958: An ingredient's status as GRAS is always vulnerable to the discovery of new evidence casting doubt on its safety. An ingredient that ceases to be GRAS falls automatically within the definition of food additive, and must then be approved by FDA for its use to be lawful.[32-A]

The FD&C Act does not prescribe procedures for determining whether an ingredient is GRAS: the statutory definition of food additive is in a legal sense self-executing. Shortly after the passage of the Food Additives Amendment, FDA issued, and from time to time has amended, a nonexclusive list of ingredients that the agency was prepared to acknowledge were GRAS--and therefore could lawfully be used without affirmative approval.[32-B] In addition, the agency has consistently acknowledged that a food manufacturer may determine for himself whether an ingredient he is considering using is GRAS.[32-C] Should a manufacturer independently conclude that an ingredient is GRAS, he runs the risk that FDA may disagree and initiate regulatory action against his product, but in such an action the agency would have to prove in court that the ingredient was not GRAS.[32-D] Neither the ingredient's absence from FDA's GRAS list nor the manufacturer's failure to consult the agency in advance would be relevant.

Under this loose system numerous food ingredients have come into common use based on the assumption by manufacturers, sometimes but no means always endorsed by FDA, that they are GRAS. FDA does not have a complete inventory of such ingredients, and it lacks good information about the extent and levels of their use.[32-E] To enhance its control over the use of GRAS ingredients an dprovide greater assurance of their safety, FDA has established a program for reviewing the available scientific data on the safety of all listed GRAS ingredients and created a formal procedure for "affirming" the GRAS status of individual substances.[33-A]

3. Ingredients previously sanctioned by USDA or FDA. The Act's definition of food additive also expressly excludes

> any substance used in accordance with a sanction or approval granted prior to the enactment of [the Food Additives Amendment] pursuant to this Act, the Poultry Products Inspection Act[33-C]. . . or the Meat Inspection Act of March 4, 1907[33-D]. . . .[33-E]

This language constitutes a genuine "grandfather" clause for food ingredients that FDA or USDA had affirmatively approved prior to the enactment of section 409 on September 6, 1958.[33-X] While FDA lacked formal authority to license food ingredients for general use prior to 1958, both it and USDA routinely responded to requests for an opinion about the safety of individual ingredients. In addition, FDA exercised premarket control over, and thus approved, the numerous ingredients permitted to be used in foods covered by standards of identity.[33-Y] USDA had issued formal regulations describing permitted uses of many ingredients in meat and poultry products,[33-F] and in some instances FDA formally acknowledged that USDA had sanctioned certain substances for food use.[34-A] Though a continuing source of controversy, the kind of documentation that is needed to establish a "prior sanction" is principally a matter of interest, for archivists. Debate can arise over the significance of specific correspondence or published articles by agency scientists in the early days of food regulation.[34-B] For present purposes it is sufficient to point out that the Food Additives Amendment excludes this class of food ingredients, of uncertain size, which enjoys a special regulatory status.[34-C]

An ingredient's prior sanction status does not depend upon a contemporary evaluation of its utility or its safety, but rests solely on the fact of prior approval by one of the two agencies. FDA has historically operated on the assumption that a prior sanctioned ingredient is permanently grandfathered, i.e., it may never become a food additive so long as it is used for the purpose for which it was sanctioned even if new evidence casts doubt on its safety.[34-D] Since the Delaney Clause only applies to food additives, this means that an ingredient that has a prior sanction is not automatically barred from use in food even if it is found to be an animal carcinogen.[34-E]

This does not mean that FDA cannot restrict the use of a prior sanctioned ingredient that new evidence demonstrates is unsafe. Foods containing such an ingredient are still subject to the basic adulteration provisions of the Act.[34-F] But the agency must be able to show that the presence of the ingredient "may render" food injurious to health under section 402(a)(1). A finding that a prior sanctioned ingredient is a carcinogen thus would permit, but it would not automatically require, FDA to terminate its use.[35-A] Furthermore, FDA has tentatively suggested that, in evaluating the appropriateness of regulatory action under such circumstances, it may consider some benefits of the ingredient's use.[35-B] Thus, the agency once indicated that the capacity of sodium nitrite to prevent the growth of botulinal tonix in cured meat products may outweigh any potential risk of cancer from preformed nitrosamines,[35-C] this assertion is legally pertinent if sodium nitrite enjoys a prior USDA sanction under the Meat Inspection Act.[35-D] From a scientific standpoint, however, there is no reason why ingredients that were formally sanctioned for use by FDA or USDA prior to September 6, 1958, should stand on a different footing, vis-a-vis Delaney, than ingredients regulated as food additives or used on the basis of a determination of GRAS status. Nor is there any persuasive theoretical basis for permitting FDA to consider the countervailing benefits of one class of ingredients but not of the others.

4. Color additives. Congress enacted the 1960 Color Additive Amendments[35-E] to assure the safety of substances used to impart color to foods, carving out yet one more category of added food constituents to which special rules apply. While the Amendments also apply to substances used to color drugs, devices, and cosmetics, the following discussion focuses exclusively on colors that are used as ingredients in food. Section 201(t)(1) of the Act defines color additive broadly:

> The term "color additive" means a material which
>
> (A) is a dye, pigment, or other substance made by a process of synthesis or similar artifice, or extracted, isolated, or otherwise derived, with or without intermediate of final change of identity, from a vegetable, animal, mineral, or other source and
>
> (b) when added or applied to a food . . . is capable (alone or thorough reaction with other substance) of imparting color thereto; except that such term does not include any material which the Secretary, by regulation, determines is used (or intended to be used) solely for a purpose or purposes other than coloring.[36-A]

FDA has adopted a regulation limiting the circumstances in which the concluding "except" clause might apply:

> For a material otherwise meeting the definition of "color additive" to be exempt from section 706 of the act, on the basis that it is used (or intended to be used) solely for a purpose or purposes other than coloring, the material must be used in a way that any color imparted is clearly unimportant insofar as the appearance, value, marketability, or consumer acceptability is concerned. It is not enough to warrant exemption if conditions are such that the primary purpose of the material is other than to impart color.[36-B]

The regulatory requirements applicable to color additives resemble those applicable to food additives, with certain important distinctions: The Color Additive Amendments require premarket safety testing and FDA approval of all substances used to color food.[36-C] The manufacturer or would-be user or a color additive may petition the agency for the issuance of a regulation permitting the color to be used in food. Before it may approve, or "list," a color, FDA must find, with reasonable certainty, that the additive poses no risk to human health, that it accomplishes its intended effect, and that its use will not result in deception of consumers.[36-D] The agency is authorized to impose restrictions on the use of a color to assure that these criteria are satisfied. Such restrictions may include limitations on levels of use,[36-E] a requirement that individual batches of the color be certified by FDA to assure that the color actually used in food is identical to the substance shown in experiments to be safe,[36-F] and specification of the foods in which a color may be used.[36-G] FDA has also taken the position that, at least in certain instances, it may require informative labeling on foods that contain a specific color additive to facilitate safe use by consumers.[37-A]

The Color Additives Amendments contain a Delaney Clause similar in language and identical in principle to the clause that appears in section 409.[37-B] This clause precludes approval for food use of any color additive shown to induce cancer when ingested by experimental animals. The Color Additive Amendments do not recognize a category of "generally recognized as safe" colors[37-C] and do not exclude from the definition of color additive substances that were sanctioned or used prior to 1960. The Delaney Clause in section 706 thus effectively applies to all food coloring agents.[37-X] Accordingly, FDA could not engage in the kind of risk-benefit analysis previously suggested for sodium nitrite as a preservative in meat in evaluating a specific color that had been shown to be an animal carcinogen.[37-D]

While Congress did not "grandfather" food colors that were already in use in 1960, it did accord them temporary special treatment. Section 203 of the Color Additive Amendments authorized FDA to list "provisionally" colors then in use that were believed to be safe, in order to allow manufacturers to conduct the kind of toxicological testing required to support approval under the scientific standards of the new law.[37-E] FDA's provisional list was designed to permit an orderly transition from a situation of bifurcated regulation in which some colors were subject to little effective control,[37-Y] to a scheme in which all color additives must be licensed. The only colors eligible for provisonal listing are those that were in use in 1960.[37-XX] Section 203 of the Amendments makes no provision for adding a new color to the provisional list to permit continued use while tests are being conducted to resolve safety questions.[37-Z]

FDA has maintained a "provisional list" of color additives for over 18 years, deleting some colors, such as Red No. 2, whose safety came under serious challenge,[38-A] and permanently listing others as scientific data were submitted to confirm their safety.[38-B] In 1977 the agency publicly committed itself to a timetable for completing testing and evaluation of the remaining provisionally listed colors, nearly 70 in all.[38-C] By the early 1980's, FDA expects that there should no longer be any provisionally listed colors; all will either have been approved or deliested.

The statutory procedures for disapproving or withdrawing approval of a lited color additive parallel those applicable to food additives, with an important difference.[38-D] If FDA, after publishing a proposal and receiving comments, issues a final order terminating the "listing" of a color, the filing of objections accompanied by a request for an evidentiary hearing automatically stays the agency's order pending completion of the hearing.[38-E] Thus FDA may not summarily terminate use of a permanently listed color on the basis of a finding of carcinogenity or some more acute hazard. By contrast, the agency can suspend use of a provisionally listed color whose safety comes into question without even publishing proposal or seeking comments.[38-F]

D. Indirect Constituents of Food

The FD&C Act separately recognizes three other categories of added food constituents that are not intentional ingredients but become components of food through their intended use in food production, processing, or distribution. The three classes are: (1) so-called "indirect" or "incidental" food additives, such as packaging materials that migrate to food; (2) animal drugs that are capable of leaving residues in tissues (meat, milk, or eggs) consumed as human food; and (3) pesticide residues on raw agricultural commodities and in processed foods.[39-X] The levels at which these indirect constituents occur typically are much lower than the levels at which most intended ingredients are used. The first two categories of constituents are subject to some version of the Delaney Clause. The statutory standards that govern establishment of tolerances for pesticide residues, however, do not accord decisive weight to a finding that a pesticide induces cancer.[39-Y]

1. Indirect food additives. As many as 10,000 substances used in proximity with food--in food packaging, in equipment used to process or store food, in compounds used to clean such equipment--in ways that permit small amounts to migrate to, and become a part of, food. Such constituents of food are ordinarily not unavoidable in the same sense that mercury contamination of swordfish is unavoidable, apparently it is not possible to find swordfish that contain no measurable amounts of mercury, but most foods can be packaged in materials that do not migrate in detectable amounts or can be marketed without packaging. Avoidance of the contaminant in the latter case does not require abandonment of the food.

The full requirements of the Food Additives Amendment apply to substances that migrate to food from food-contact surfaces. Section 201(s) of the Act defines a food additive as

> any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food. . . .[40-A]

A migtating rood contact material can escape food additive classification if it is GRAS or if it is the subject of a prior sanction, and some established packaging materials fall within these exceptions.[40-B] The procedures for obtaining, or withdrawing, FDA approval are identical for indirect and direct food additives, and the basic statutory criteria for approval are the same. Accordingly, an indirect food additive must be shown, with reasonable certainty, to be safe, and no weight may be accorded the economic benefits of its use. Similarly, the Delaney Clause squarely applies no indirect food additives, and prohibits the use, in applications that are likely to result in migration to food, of any substance that has been shown to induce cancer in experimental animals. While application of the Delaney Clause has proved controversial in the context of direct ingredients and animal drugs, its potential impact on indirect food additives is likely to prove the most disruptive.

The majority of materials used in packaging and other food-contact applications would never be considered for use as food ingredients because their chemical structure or experimental evidence would suggest they would pose a high risk of toxic effects. This would clearly be true for the many varieties of packaging materials synthesized from hydrocarbon sources. Furthermore, rapid improvements in the techniques of chemical analysis have permitted scientists to measure increasingly small quantities of substances migrating from food contact applications.[41-A] This development has made it possible to detect in food traces of packaging materials that once were thought to be incapable of migration. Improvements in analytical chemistry are thus irresistably enlarging the category of compounds that are potential food additives--and subject to the Delaney Clause.[41-B]

A recent decision of the FDA Commissioner, if upheld on judicial review, threatens to accelerate this development.[41-C] The decision involves the use[41-D] of acrylonitrile copolymers to manufacture containers beverage. FDA initiated proceedings to revoke outstanding food additive regulations for four similar containers, based on evidence that (1) residual acrylonitrile monomer was likely to migrate into the beverages at levels higher than anticipated, and (2) recent experimental data raised serious questions about the material's safety.[41-E] The container manufacturers contended that improved fabrication methods would produce a bottle containing so little residual acrylonitrile monomer that no migration could be detected. The Commissioner rejected this contention, essentially as unresponsive. He ruled that a material in packaging can be presumed "to become a component of food," within the meaning of section 201(s), even though no migration is detectable by available methods of analysis if evidence demonstrates that the material is capable of diffusing into packaged food.[41-F] This presumption may be defeated only if the petitioner can prove that diffusion does not occur when lower concentration of the material are present.[41-G]

The Delaney Clause is likely to be frequently implicated in regulatory decisions involving indirect additives because many chemicals used in the manufacture of food contact materials are suspect or unequivocal carcinogens. This discovery is partly a result of accumulating evidence of the effects of industrial exposure, as in the case of workers engaged in the manufacture of vinyl chloride and acrylonitrile.[42-A] It is also a product of demands for toxicological evaluation of industrial chemicals that have been stimulated by other regulatory agencies, notably the Occupational Safety and Health Administration[42-B] and the Environmental Protection Agency.[42-C]

Scientific developments on two fronts are therefore likely to precipitate application of the Delaney Clause to compounds whose presence in food could not have been predicted, much less detected, only a few years ago. Unlike most intentional ingredients, these new food additives, such as acrylonitrile, are only found (if at all) at the very low parts per billion range in packaged food. Enforcement of the Food Additives Amendment in this context may produce unexpected results. The Delaney Clause squarely forbids use of a carcinogenic material for food packaging if it likely to migrate to food in any quantity[42-E] and it could reach other, more remote, uses of the material, such as food conveyor belts and water pipes made from vinyl chloride.[42-F] Furthermore, section 409 does not allow any showing of an additive's special utility to overcome a finding of carcinogenicity. The law appears to make no allowance for the fact that the risk posed by migrating quantities of food packaging material, though not negligible, is likely to be much lower than that posed by most direct food additives, which are used at much higher levels.[43-A]

2. Animal drug residues. Compounds administered to food producing animals in the form of drugs or feed supplements comprise a second category of indirect constituents of human food for they may leave residues in meat, milk, or eggs derived from the animals. Animal drugs and animal feed additives are both subject to the Delaney Clause, but with an important qualification created by a special amendment to the clause passed by Congress in 1962. Before examining this qualification, a brief summary of the regulatory framework for animal drugs and feed additives is in order.

Compounds added to the feed of animals are subject to the Food Additives Amendment of 1958 on the same terms as intentional ingredients of human food; the Act's definition of "food" specifically embraces "articles used for food or drink for man or other animals. . . ."[44-A] Accordingly, a substance added to animal feed must be GRAS, or be used in accordance with a prior sanction issued by FDA or USDA, or be the subject of an approved food additive regulation. The procedures for approval of animal feed additives generally do not differ from applicable ingredients of human food.[44-B] The central inquiry is usually whether the ingredient will be safe for the animals to which it will be fed. However, FDA has not undertaken a formal review of the safety of animal feed, nor has it established any system for affirming specific ingredients as GRAS.[44-C]

Prior to the passage of the Animal Drug Amendments of 1968,[44-D] drugs intended for administration to animals were potentially subject to the general requirements of section 505, applicable to all new drugs, veterinary as well as human.[44-E] This provision, from 1962 on, required that a new animal drug be shown to be safe as well as effective for the animals to which it was to be administered.[44-X] Furthermore, if a drug was to be used in food producing animals in a fashion that could result in residues in the edible tissues, it also had to meet the food safety requirements of the Food Additives Amendment.[45-A] The 1968 Amendments established a consolidated licensure procedure, but did not alter the substantive standards applicable to animal drugs that may contaminate human food.[45-B]

The standards applicable to drugs used in food producing animals thus require FDA to balance the risks and benefits of a drug for the target animals and to verify the safety vel non of any residues that might occur in food. For an animal feed additive, the agency must evaluate the safety of the compound under the criteria prescribed by section 409, including the Delaney Clause. As they apply to animal drugs and feed additives, however, the criteria underwent a significant change in 1962. Following the passage of the Food Additives Amendment in 1958, FDA concluded that no compound found to induce cancer in laboratory animals could be approved for use as an additive to animal feed on the unexceptionable ground that the Delaney Clause prohibited the approval of any carcinogenic "food additive." This interpretation precluded the marketing of a number of compounds that promised significant savings in the cost of producing livestock. Moreover, it had the effect of preserving a monopoly for manufacturers of implantable dosage forms of such compounds, which could escape the food additives law if FDA concluded that they could not "reasonably be expected to become a component of food."[45-X] The notable example was diethylstilbestrol (DES), a synthetic estrogen believed to be an animal carcinogen.[45-C] As part of the Drug Amendments of 1962, Congress addressed these problems by adding the following, qualifying language to the flat prohibition of the Delaney Clause:

> . . . [T]his proviso shall not apply with respect to the use of a substance as an ingredient of feed for animals which are raised for food production, if the Secretary finds (i) that, under the conditions and reasonably certain to be followed in practice, such additive will not adversely affect the animals for which such feed is intended, and (ii) that no residue of the additive will be found (by methods of examination prescribed or approved by the Secretary by regulations . . . in any edible portion of such animal after slaughter or in any food yielded by or derived from the living animal . . . .[46-A]

Known as the "DES proviso," this language requires FDA to prescribe analytical methods for measuring residues of a carcinogenic drug or feed additive in animal tissues (meat, milk, and eggs) used for human food. This amended version of the Delaney Clause is implemented through the procedures for licensing animal feed additives and new animal drugs.[46-B] Under current FDA practice, the manufacturer of a new animal drug or animal feed additive that might be a carcinogen must conduct chronic toxicity tests of the compound (and selected matabolites) to determine whether the Delaney Clause applies to the product. If the drug is found to induce cancer,[46-C] the manufacturer must submit acceptable chemical analytical and confirmatory methods as a condition of approval.

The formal administrative process for the approval of new animal drugs resembles that for human food and animal feed additives, providing comparable opportunities for a formal evidentiary hearing on any denial of approval and for judicial review.

Essentially the same procedures must be followed if FDA wishes to withdraw approval of a compound on the ground that it fails to meet the requirements of the modified Delaney Clause or is otherwise unsafe for humans.[47-A]

Before approving a new animal drug FDA must be satisfied that it has been shown to be effective for its intended uses in target animals (including, if pertinent, growth promotion), that it will be safe for the animals, and, if the animals are sources of human food, that any residues will, with reasonable certainty, be safe for human consumption.[47-B] In applying the first two criteria, the agency engages in a rough risk-benefit analysis of the same kind it performs in evaluating drugs for human use. The third criterion, however, embodies the basic safety standard of the Food Additives Amendment, which, in the agency's view, does not permit balancing any risk to human health against benefits provided to animal husbandry or food production.[47-C] In substance, the drug residue is treated simply as another type of indirect feed additive. Accordingly, if an animal drug would leave unsafe residues in food FDA would not approve it even if its use might lower production costs, reduce meat prices, or control animal disease. The agency has never seriously considered requiring labeling of meat derived from treated animals to alert consumers to the potential risks from drug residues.[47-D] Moreover, most meat and many poultry products packaged at the point of sale, which would make it difficult to enforce such a labeling requirement comprehensively.

The Act does not accord special treatment to residue-producing animal drugs based upon their prior use, as it does for certain classes of intentional ingredients of human feed or animal feed.[47-E]

The law does not require premarketing approval of animal drugs that are generally recognized as safe and effective,[47-F] and it does "grandfather" certain products marketed prior to 1938 or 1962.[48-A] As a practical matter, however, neither escape route is available to most currently marketed animal drugs that are capable of leaving residues in human food nor would they be open to any new product. Accordingly, the modified Delaney Clause can be considered potentially applicable to almost all drugs used in food producing animals, a significant number of which are suspected laboratory animal carcinogens.[48-B]

Precisely for this reason Congress' 1962 modification of the Delaney Clause has been the subject of continuing controversy. FDA has assumed that the amended clause does not automatically forbid approval of a carcinogenic drug or animal feed additive simply on finding that its use may result in some residues, however small. Rather, the agency's position is that the law permits approval if the sponsor submits analytical methods exist that are capable of measuring--and thereby controlling--any residues that may be unsafe.[48-C] Until 1977, however, FDA had not adopted formal criteria for evaluating analytical methods offered as a means of controlling unsafe residues. It reviewed each new drug individually and, generally, required that no residues should be detectable by the best analytical method then available.[48-D] Because some animal drugs have been tested chronically and found to be carcinogenic only after they were initially marketed, however, a few remain approved on the basis of assay methods that are less sensitive than might now be prescribed.[48-E]

Improvements in analytical chemistry have had almost as dramatic an impact on FDA's efforts to control animal drug residues as on its regulation of indirect food additives. The agency has initiated proceedings to withdraw approval of DES implants because the drug has been found to leave measurable residues at levels that cannot be detected by the methods accepted a decade ago.[48-F] And, as in the case of indirect food additives, the increasing capability of analytical methods to measure ever smaller residues will enlarge the universe of animal drugs and feed additives that are subject to the strictures of the modified Delaney Clause.[49-A] By contrast with the Delaney Clause itself, the DES proviso focuses on the *detection* of residues in edible animal tissues, rather than on the *addition* of the compound to animals or their feed. This focus of the legislative draftsmen has enabled FDA to address the issue of carcinogenic animal drugs and feed additives in a fashion that might also be applied to other classes of indirect food constituents.[49-B] In a February 1977 regulation, *Criteria and Procedures for Evaluating Assays for Carcinogenic Residues in Edible Products*,[49-C] the agency announced the standards it would apply in determining the level of residues an assay for a carcinogenic animal drug or feed additives must be capable of measuring if the compound is to be approved. To dramatize its impact the regulation can be described as establishing the criteria FDA would follow in deciding what residues may safely be allowed to go undetected.[49-D]

The February 1977 regulation embodied several basic requirements:

1. It mandated chronic testing of any compound that FDA concluded had the potential to leave carcinogenic residues in human food.[49-E]

2. It prescribed an extrapolation from the results of positive chronic tests, i.e., tests that demonstrate carcinogenicity, to project the level of potential residues in the average diet (of meat, milk, or eggs) that corresponds to a 1 in 1,000,000 individual lifetime risk of cancer. The regulation characterized this risk as "acceptable," apart from pointing out though that the risk was small, and only one of many to which individuals are exposed, the agency did not explain the basis for this judgment.[49-F]

3. Finally, the regulation specified that before a compound could be approved, the sponsor would have to provide FDA with a practicable[50-A] assay method that was capable of measuring residues at a level that would assure no individual was exposed to greater than the extrapolated "acceptable" risk.[50-B] To increase confidence that actual residues would not exceed the level prescribed, the drug's labeling would specify the period prior to slaughter, scientifically determined, during which the drug should not be administered or implanted.[50-C] In substance, the agency was saying that if the potential residues in feed of a carcinogenic animal drug would not increase any individual's risk of getting cancer by more than 1 in one million, those residues could be ignored.

The February 1977 regulation did not contemplate that FDA would engage in balancing the risks and benefits of the animal drugs or feed additives. It focused on only one element of the risk-benefit equation, and specified a maximum level of risk--theoretically expressed in terms of the level of drug residues that the approved assay method might fall to detect--which the agency would consider "acceptable." For most carcinogenic animal drugs and feed additives the assay sensitivity dictated by the regulation--and thus the level of "permitted" undetectable residues--would be in the very low parts per billion range. This would strain and probably exceed the capability of most analytical methods currently approved for animal drugs. In addition, relying on Congress' objective in enacting the original Delaney Clause,[50-D] the regulation specified that if a practicable assay were developed that was more sensitive than originally demanded by its criteria, FDA would require the new method to be used.[50-E] FDA's recent approach to controlling residues of animal drugs and feed additives therefore does not entirely avoid the pressures to regulate more stringently that created by continued improvements in assay sensitivity.[50-F]

3. Pesticide residues. Residues of chemicals used to control animals and insects that threaten crops constitute a third class of substances that are not desired, but are nonetheless expected, constituents of foods. Pesticide residues often remain on raw agricultural commodities after harvesting and preparation for consumer purchase without further processing. Residues may also occur in processed foods made from raw commodities to which pesticides have been applied. As outlined below, the present law treats these two situations differently.[51-A]

Federal regulation of pesticide residues differs from the pattern applicable to the several categories of food constituents previously discussed because primary responsibility for determining permitted levels of human exposure rests with the Environmental Protection Agency, not with FDA.[51-B] Most pesticides are subject to regulation under two statutes. The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)[51-C] requires licensure, of any pesticide distributed for use in the United States. Sections 408 and 402(a)(2)(B) of the FD&C Act forbid the distribution of raw or processed foods bearing pesticide residues that have not been sanctioned by EPA.[51-D] The safety of food for human consumption is the focus of the latter provisions.

Under FIFRA, every pesticide used in the United States must be "registered," i.e., licensed, by EPA.[51-E] That statute mandates that a pesticide "shall" be registered if, in addition to meeting other requirements not pertinent here, "when used in accordance with widespread and commonly recognized practice it will not generally cause unreasonable adverse effects on the environment."[51-F]

Congress has further defined this standard to mean 'any unreasonable risk to man or the environment, taking into account the economic, social and environmental costs and benefits of the use of any pesticide."[52-A] Under this broad language EPA considers the full range of a pesticide's possible health effects, including its potential to induce cancer.[52-B] Against these risks, EPA is empowered, indeed obligated, to weigh the utility of a pesticide in eradicating pests and promoting food production.[52-C] FIFRA does not preclude registration of a pesticide that has been shown to induce cancer in laboratory animals, although EPA has relied on such evidence to terminate registration of several compounds, and has established a presumption against initial or continuing registration of pesticides that are frank or suspect animal carcinogens.[52-X] In the registration process, EPA is concerned principally with the health of persons exposed to the pesticide during its application, while harvesting or transporting crops, or in the environment generally. It addresses the risks of the compound as a potential contaminant of food under sections 408 and 409 of the FD&C Act.

A pesticide that is applied to a commodity produced for human food consumption might "reasonably be expected to become a component"[52-D] of food, whether the commodity is marketed in a raw state or after further processing. To avoid classifying pesticide residues as food additives, the statutory definition includes a limited exception for pesticide chemicals "in or on a raw agricultural commodity," and thus exempts such constituents of food from the requirements of Section 409.[52-E] At the same time, section 402(a)(2)(B) of the Act provides that a food is adulterated "if it is a raw agricultural commodity and it bears or contains a pesticide chemical which is unsafe within the meaning of section 408(a)."[52-F] This provision was added to the Act in 1954 as part of the legislation designed to authorize FDA, originally, to establish tolerances for residues on raw agricultural commodities of pesticides that had been registered under FIFRA.[52-G] This authority appears in section 408 of the Act, pursuant to which EPA determines the quantity of a pesticide that may remain on a raw commodity when it is introduced into interstate commerce.

While FIFRA requires registration of all pesticides, section 408(a) of the FD&C Act requires a tolerance only for "any poisonous or deleterious pesticide chemical, or any pesticide chemical which is not generally recognized . . . as safe for use. . . ."[53-A] Accordingly, residues of a pesticide that would be considered GRAS do not require formal government approval.[53-B]

Section 408(b) prescribes the criteria EPA must apply in establishing tolerances:

> . . . [T]he Secretary shall give appropriate consideration, among other relevant factors, (1) to the necessity for the production of an adequate, wholesome, and economical food supply; (2) to the other ways in which the consumer may be affected by the same pesticide chemical or by other substances that are poisonous or deleterious; and (3) to the opinion of the Secretary of Agriculture as submitted with a certification of usefulness [of the pesticide]. . . . In carrying out the provisions of this section relating to the establishment of tolerances, the Secretary may establish the tolerance applicable with respect to the use of any pesticide chemical in or on any raw agricultural commodity at zero level if the scientific data before the Secretary does not justify the establishment of a greater tolerance.[53-C]

Conspicuously, this language does not mention the risk of cancer, and since a pesticide residue on a raw commodity is excepted from the definition of a food additive,[53-D] the Delaney Clause does not apply. EPA could, therefore, establish a finite tolerance for a pesticide that has been shown to induce cancer in experimental animals (or indeed in man) but that, because of its utility, remains eligible for registration under FIFRA.[54-A] In short, the Act permits the approval of constituents of food--residues of pesticides on raw commodities--that could not lawfully be added as direct ingredients. This inconsistency is amplified by the Act's distinctive treatment of pesticide residues in processed foods.

While many types of processing substantially reduce the levels of pesticide residues on raw agricultural commodities, few processes eliminate all such residues.[54-B] Congress therefore recognized that some provision had to be made for controlling pesticide residues that persisted on raw commodities used to make finished foods, e.g. canned vegetables. The reader will recall that the exception in the Act's definition of food additive for pesticide chemicals extends only to residues "in or on a raw agricultural commodity."[54-C] A pesticide residue on a processed food, unless it is GRAS or prior sanctioned, is therefore a food additive which would render the food adulterated if there were no regulation approving its presence.[54-D]

Any residue in a processed food of a pesticide for which EPA has not established a tolerance on the raw commodity renders the food adulterated under section 402(a)(2)(C) of the Act.[54-E] But if a tolerance for the pesticide on the raw commodity has been established, Congress has dispensed with the requirement for approval of the pesticide in the processed food under section 409--if certain conditions are met.[54-F] These conditions are set out in a proviso to section 402(a)(2)(C) added in 1958, which states:

> *Provided*, That where a pesticide chemical has been used in or on a raw agricultural commodity in conformity with an exemption granted or a tolerance prescribed under section 408 and such raw agricultural commodity has been subjected to processing such as canning, cooking, freezing, dehydrating,

> or milling, the residue of such pesticide chemical remaining in or on such processed food shall, notwithstanding the provisions of sections 406 and 409, not be deemed unsafe if such residue in or on the raw agricultural commodity has been removed to the extent possible in good manufacturing practice and the concentration of such residue in the processed food when ready to eat is not greater than the tolerance prescribed for the raw agricultural commodity. . . .[55-A]

The Act thus provides a pass through for pesticide residues for which a tolerance has been established if that tolerance is not exceeded when the raw commodity is processed. This means that if EPA establishes a finite tolerance for a carcinogenic pesticide on a raw commodity, that pesticide may lawfully appear in the processed food in a quantity that does not exceed the tolerance--"notwithstanding," as the proviso states, the Delaney Clause.

One further example illustrates the exquisite, if arcane, interrelationship between section 409 and the provisions of the Act applicable to pesticides. Although processing may reduce residues of a pesticide present on a raw commodity, sometimes such residues instead become concentrated as processing shrinks the volume of solid material.[55-B] When this occurs, the proviso to section 402(a)(2)(C) is not satisfied and the quantity of the pesticide that exceeds the section 408 tolerance is considered a food additive.[55-C] In such a case, a distributor of the processed food requires a food additive regulation to prevent the food from being adulterated and, to obtain such a regulation, must demonstrate, with reasonable certainty, that the quantity of the pesticide is safe.[56-A] Many food additive regulations authorizing concentrated residues of pesticides have been promulgated by EPA, which also has responsibility for implementing this facet of the Food Additives Amendment because it is the recipient of the safety data submitted to support tolerances under section 408.[56-B]

A simple example will illustrate the intricate interworkings of the current law. Suppose that EPA has established a tolerance for a pesticide on raw cabbage at 10 parts per million. Suppose further that the pesticide has been shown in animal experiments to induce cancer but, because of its importance in controlling crop pests, EPA maintains its registration. Under the proviso to section 402(a)(2)(C), up to 10 ppm of this carcinogenic "additive" may lawfully appear in food. But if residues of the pesticide concentrated during processing, any quantity in excess of 10 ppm would constitute an "unsafe food additive" and, under the Delaney Clause, presumably could not be approved.[56-C] However, if EPA were to raise the tolerance for raw cabbage to a level that the residues in the processed cabbage would not exceed,[56-D] in a legal sense the food additive would disappear--and the Delaney Clause would not preclude marketing of the cabbage!

It should be noted that even establishment of a zero tolerance for a carcinogenic pesticide does not assure that no residues whatever will appear on the raw commodity or in processed food. Effective enforcement of a zero tolerance depends on the observance by growers and food producers of meticulous processing standards and requires intensive monitoring. FDA simply does not have the inspectional resources to be able to guarantee that some lots of commodities containing measurable, and thus illegal, pesticide residues do not reach consumers. Moreover, even lot-by-lot monitoring would be constrained by the limits of the analytical methods for measuring pesticide residues. In reality, therefore, a zero tolerance may be considered a finite tolerance, established at the level that can be measured by available analytical methods. This is true for any unintended constituent of food whose occurrence cannot be effectively controlled or whose benefits are thought to preclude abandonment of its use.

The administrative procedure for obtaining a tolerance for residues of a pesticide on a raw commodity resembles the procedure for obtaining approval of a food additive, with two significant differences: (1) A petitioner for a tolerance must obtain from the Secretary of Agriculture a certification that the pesticide is "useful" for the purpose for which the tolerance is sought.[57-A] (2) EPA on its own initiative may, or at the request of the petitioner must, submit a petition to an advisory committee of experts appointed by the National Academy of Sciences for evaluation and recommendation.[57-B] An opportunity for a formal evidentiary hearing is provided before EPA may refuse to establish a tolerance, although few petitioners have ever requested a hearing.[57-C] The same procedures must be followed by EPA in revoking or modifying a tolerance once established. The procedures EPA must follow when it is petitioned to promulgate a food additive regulation authorizing the presence on a processed food of a residue in excess of that sanctioned for the raw commodity are the same as those that apply to FDA.[57-D]

BB-71

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MERRILL FOOTNOTES

I. Introduction

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1-A Statement of Sherwin Gardner, Acting Commissioner of Food and Drugs, March 9, 1977.

1-B 21 U.S.C. § 321. Hereafter the basic statute is referred to as "the Act" or "the FD&C Act."

1-C 21 U.S.C. § 321 et seq. The original Delaney Clause appears in section 409(c) of the Act, 21 U.S.C. § 348(c), and reads as follows:

> Provided, That no additive shall be deemd to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal . . . .

As explained in more detail in subsequent sections this functionally identical language also appears in the provisions of the Act dealing with color additives and drugs administered to animals used to produce human food. See notes ______, infra and accompanying text.

1-D For descriptions of the reaction, see, e.g., The Great Saccharin Snafu, Consumer Reports (Jul 1977), at p. 410; Demkovich, Saccharin's Dead, Dieters Are Blue, What is Congress Going to Do?, National Journal, June 4, 1977, at p. 856; Wolff, Of Rats and Men, New York Times Magazine, May 15, 1977, at p. ; Hines and Randal, Behind the Saccharin Uproar, The Progressive, June 1977, at p. 13. Epitomizing the exaggerated reaction of many non-scientists was the proposal of Congressman Andrew Jacobs to amend the law to permit the continued sale of saccharin accompanied by the warning: "The Canadians have determined saccharin is dangerous to your rat's health." See Cancer and Your Sweet Tooth, New Republic, April 11, 1977, at p.

1-E Pub. L. 95-203, 91 Stat. 1451 (November 23, 1977). For discussions of Congress' motives, see H.R. Rep. No. 95-658, October 8, 1977; S. Rep. No. 95-353 July 19, 1977.

2-A Saccharin Study and Labeling Act, § 2.

3-AA See R. Kingham, Statutory and Administrative Theories by Which FDA Avoids Applying the Delaney Clause (November 10, 1977) (unpublished).

3-A Pure Food and Drugs Act of 1906, 34 Stat. 768, repealed 52 Stat. 1059 (1938).

3-B See, in historical sequence, § 402(a) of the Federal Food, Drug, and Cosmetic Act of 1938, Pub. L. 717, 75th Cong., 3d Sess., now codified at 21 U.S.C. § 342(a); Pesticide Residue Amendments of 1954, Pub. L. 518, 84rd Cong., 2d Sess., now codified at 21

U.S.C. § 346a; Food Additives Amendment of 1958, Pub. L. 85-929, 85th Cong., 2d Sess., now codified at 21 U.S.C. § 348; Color Additive Amendments of 1960, Pub. L. 86-618, 8th Cong., 2d Sess., now codified at 21 U.S.C. § 376; and Animal Drug Amendments of 1968, Pub. L. 90-399, 90th Cong., 2d Sess., now codified at 21 U.S.C. § 360b.

II.A. The Food Safety Provisions of the Act

4a-A Federal Food and Drugs Act of 1906, § 7, 34 Stat. 768 (1906).

4a-B 21 U.S.C. § 342(a)(1).

4a-C Id. For a discussion of the legislative history of this provision, see note 11-C infra.

4b-A 21 U.S.C. § 346 (originally 406(a) of the Act).

4b-B See the discussion at text accompanying notes 15A-15C infra.

4c-A 21 U.S.C. § 346a. Pub. L. 518, 83rd Cong., 2d Sess., 68 Stat. 511 (1954).

4c-B 21 U.S.C. § 342(a)(2)(B).

4c-C See 21 U.S.C. § 346a(d)-(h) and text accompanying notes infra.

4c-D 21 U.S.C. § 348. Pub. L. 85-929, 85th Cong., 2d Sess., 72 Stat. 1784 (1958).

4c-E 21 U.S.C. § 321(s).

4c-F 21 U.S.C. § 342(a)(2)(C).

4c-G 21 U.S.C. § 321(s). For a detailed discussion of the Food Additives Amendment, see text accompanying notes 26B-35D infra.

4d-A See 21 U.S.C. § 321(t).

4d-B See § 406(b) of the original 1938 Act, which was repealed in 1960. For a detailed discussion of FDA's implementation of this provision, see Flemming v. Florida Citrus Exchange, 358 U.S. 153 (1958).

4d-C See text accompanying note 4c-B supra.

4d-D Pub. L. 86-618, 74 Stat. 397, 86th Cong., 2d Sess., (1960). The Color Additive Amendments are now codified principally at 21 U.S.C. § 376.

4d-E 21 U.S.C. § 342(c).

4d-F Pub. L. 90-399, 82 Stat. 341, 90th Cong., 2d Sess. (1968). The Animal Drug Amendments are now codified principally at 21 U.S.C. § 360b.

4d-G See generally H.R. Rep. No. 875, 90th Cong., 2d Sess. (1968); S. Rep. No. 1308, 90th Cong., 2d Sess. (1968).

4d-H 21 U.S.C. § 360b.

4d-I See 21 U.S.C. §§ 342(a)(2)(D), 360b(a)(1).

4e-A See Poisonous or Deleterious Substances in Foods, 39 Fed. Reg. 42743, 42744 (1974).

4f-A For example, FDA estimates that the consumption of one can each day of a soft drink sweetened with saccharin increases the risk of bladder cancer of between zero and 4 in 10,000. See Saccharin and Its Salts, 42 Fed. Reg. 19995, 20001 (1977). By contrast, by the agency's own estimate, the risk of cancer associated with consumption of peanut products bearing permitted levels of aflatoxin contamination is ______________________________ See [citation to be obtained].

II.B. History & Impact of the Delancy Clause

5-A 15 U.S.C. § 348(c)(3)(A)(1976). See C. W. DUNN, LEGISLATIVE RECORD OF 1958 FOOD ADDITIVES AMENDMENT TO FEDERAL FOOD, DRUG, AND COSMETIC ACT (CCH FOOD LAW INSTITUTE SERIES, 1958).

5-B 21 U.S.C. § 342(a)(1)(2)(1976).

5-C Pesticide residues on raw agricultural commodities were an exception to this general statement. In 1954, Congress had established a system for "licensing" pesticide residues that had been shown to be safe. Pub. L. No. 83-518, 68 Stat. 511 (Codified at 21 U.S.C. §§ 321, 342, 346a (1976). See *supra* note ____, and accompanying text.

5-D *See* 21 U.S.C. § 346 (1976); Poisonous or Deleterious Substances in Feed, 39 Fed. Reg. 42743, 42744 (Dec. 6, 1974).

5-E Section 409(c) of the 1958 Food additives Amendment provides:

> "(c)(1) The Secretary shall--
>
> > (A) by order establish a regulation . . . prescribing, with respect to one or more proposed uses of the food additive involved, the conditions under which such additive may be safely used.
>
> (3) No such regulation shall issue if a fair evaluation of the data before the secretary--(A) fails to establish that the proposed use of the food additive, under the conditions of use to be specified in the regulation, will be safe: *Provided*, that no additive shall be deemed to be safe if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal. . . ."

5-F *Hearings before the House Select Committee to Investigate Use of Chemicals in Foods and Cosmetics*, 81st Cong., 1st & 2d Sess.

and 82d Cong., 1st Sess. (1950-1952) (popularly known as the "Delaney Committee" hearings); see H.R. Rep. No. 2356, 82d Cong., 2d Sess. (1952).

5-G Pub. L. No. 83-518, supra note 5-C.

6-A H.R. 13254, 85th Cong., 2d Sess. (1958).

6-C 104 Cong. Rec. 17412, 17415 (1958). The letter from the Department withdrawing the agency's objection to the Delaney clause stated in part:

> "The widespread interest in cancer led to suggestions that the food additives legislation should mention the disease by name and forbid the approval of any substance that is found upon test to cause cancer in test animals. This Department is in complete accord with the intent of these suggestions. . . . H.R. 13254, as approved by (the) committee, will accomplish this intent. . . . To single out one class of diseases for special mention would be anomalous and could be misinterpreted. Hence, . . . we chose general language that would restrain use of any additive that would have an adverse effect on the public health.
>
> At the same time, if it would serve to allay any lingering apprehension on the part of those who desire an explicit statutory mandate on this point, the Department would interpose no objection to appropriate mention of cancer in food additives legislation.

Id.

6-D 21 U.S.C. § 348(c)(3)(A) (1976).

6-E 21 U.S.C. § 376(b)(5)(B) (1976).

6-F 21 U.S.C. § 360b(d)(1)(H) (1976).

6-G All three provisions prohibit use in products that may be swallowed of substances which are shown to induce cancer when ingested by man or animal or are shown to induce cancer by other appropriate tests. Thus, administration of an additive by a route other than ingestion must be determined, in the first instance by FDA, to be "appropriate" by qualified experts before the Delaney clause applies. The clause applicable to color additives bars the approval of a carcinogenic color for any use "which will or may result in ingestion of all or part of such additive." This language would leave open the possible use of carcinogenic color to enhance the appearance of certain parts of foods (e.g., husks, rinds, shells) if it were certain the color would not contaminate edible portions of the food.

The food Additives Amendment permits the approval of a carcinogenic additive for use in animal feed if the additive will neither adversely affect the animals nor leave any measurable residue in edible portions of slaughtered animals or in food yielded by living animals. A similar exception is made for carcinogenic animal drugs which neither harm animals nor leave residues in food products derived from treated animals. See 21 U.S.C. 348(c)(3)(A). This exception to the Delaney Clause is explored in detail at pp._________, infra.

6-H 21 U.S.C. § 348(c)(3)(A).

6-HH During hearings on the Color Additive Amendments, Secretary of Health, Education and Welfare ARthur Flemming endorsed the conclusion of a National Cancer Institute report that: "No one at this time can tell how much or how little of a carcinogen would be required to produce cancer in any human being, or how long it would take the cancer to develop." Color Additives: Hearings on H.R. 7624 Before the House Comm. on Interstate and Foreign Comm., 86th Cong., 2d Sess. 61 (196). He went on to state that:

> We have no basis for asking Congress to give us discretion to establish a safe tolerance for a substance which definitely has been shown to produce cancer when added to the diet of test animals. We simply have no

> basis on which such discretion could be exercised because no one can tell us with an assurance at all how to establish a safe dose of any cancer-producing substances.

Id. at 62. *See* Blank, *The Delaney Clause: Technical Naivete and Scientific Advocacy in the Formulation of Public Health Policies*, 62 Cal. L. Rev. 1084 (1974); Turner, *The Delaney Anticancer Clause: A Model Environmental Protection Law*, 24 Vand. L. Rev. 889 (1971).

6-I "[T]he opposition to inclusion of an anticancer clause arises largely out of a misunderstanding of how this provision works. It allows the Department and its scientific people full discretion and judgment in deciding whether a substance has been shown to produce cancer. . . ." *Color Additives: Hearings on H.R. 7624 and S. 2197 Before the House Comm. on Interstate and Foreign Commerce*, 86th Cong., 2d Sess. 501 (1960) (Statement of HEW SEcretary Arthur S. Flemming).

7-A Controversy continues to rage over the appropriateness of feeding laboratory animals large doses of a substance to compensate for their short life span and the relatively small number that can practicably be included in a single experiment. Congressman James G. Martin (R.-N.C.) was extremely critical of the rodent studies on which FDA relied in proposing a ban on saccharin:

> [S]accharin causes no significant increase in cancer of the test rats if they were fed massive overdoses every day from the moment of birth, and . . . no significant increase in bladder cancer resulted from exposure where the rat and its pregnant monther were fed 2 percent of their diet, that is 1 gram of saccharin per kilogram of body weight, daily. Thus, only with the "double whammy," of 2.5 grams per kilogram daily for two generations, was there a significant effect. That does not translate into much of a risk to humans.

123 Cong. Rec. H 11,066 (daily ed. Oct. 17, 1977). Mr. Martin went on to argue that:

> [The carcinogenic effect is] perhaps due to the action of that overdose of saccharin as being a physical irritant, one which would increase the raw sensitivity of the rat's bladder tissue. The mechanism may be a secondary effect in which this massive, extreme, overdose would affect the rat's detoxification mechanism. Either way [cancer] only occurs at a near lethal overdose.

123 Cong. Rec. E 6414 (daily ed. Oct. 17, 1977). See Martin Criticizes Conclusions of MIT Study, 20 Food Chemical News 29 (1978).

7-B In practice, FDA has rarely relied solely on the Delaney Clause in attempting to ban, or restrict exposure to, carcinogenic food ingredients. Between the early 1950's and 1977 the agency had forbidden the use of fourteen food constituents on the grounds they caused cancer in laboratory animals. (In only three instances--involving Flectol H, Chroanaline, and saccharin--did it expressly invoke the Delaney Clause.) This total does not include more recent FDA actions dealing with chloroform and acrylonitrile. See Agriculture-Environmental, and Consumer Protection Appropriations for 1975, Hearings Before a Subcommittee of the House Committee on Appropriations, 93rd Cong., 2d Sess. [438-445] (1974).

7-C FDA allowed use of the nutrient, selenium, in animal feed although some studies indicated it is a potential carcinogen. The rationale for this decision was that at certain dose levels the additive induced a pathologic change (i.e., liver damage) in test animals, which in turn led to cancer. FDA maintained that the anticancer clause did not preclude approval of the additive for use at levels which provide an adequate margin of safety below the dose at which pathologic changes occur. 38 Fed. Reg. 10458 (1973); 39 Fed. Reg. 1355 (1973).

7-D This was the basis of FDA's recent rejection of a petition by the Health Research Group which sought revocation of approval for several color additives. 43 Fed. Reg. 54990 (1978). See Acrylonitrile Copolymers Used to Fabricate Beverage Containers, Final Decision, 42 Fed. Reg. 48528 (1977).

7-E 21 C.F.R. § 170.20(a) (1978) states:

> In reaching a decision on any petition filed under section 409 of the act, the Commissioner will give full consideration to the specific biological properties of the compound and the adequacy of the methods employed to demonstrate safety for the proposed use, and the Commissioner will be guided by the principles and procedures for establishing the safety of food additives stated in current publications of the National Academy of Sciences-National Research Council. . . .

See FDA Advisory Committee on Protocols for Safety Evaluation, Panel on Carcinogenesis Report on Cancer Testing in the Safety Evaluation of Food Additives and Pesticides, 20 Toxicol. Appl. Pharmacol, 419 (1971).

7-F See note 7-E, supra; 21 C.F.R. § 500.80(b) (1978); Provisionally Listed Color Additives, 42 Fed. Reg. 6992, 6994 (1977).

8-A See Saccharin and Its Salts, 42 Fed. REg. 19996 (1977). The Act does not specify how soon FDA must act to ban an approved additive that is later found to be carcinogenic. This silence has permitted the agency to argue, in correspondence with the Department of Justice concerning the additive sodium nitrite, that use of the ingredient may be phased out while efforts are made to find an alternative means of preventing botulism. See Culliton, Nitrites--to ban or not to ban, 1978 British Medical Journal 1613; Smith, Ever So Cautiously, the FDA Moves Toward a Ban on Nitrites, 201 Science 887 (1978). However, it is clear that § 409(a)(3)(A) precludes FDA from allowing any use whatever of a new additive that is shown to induce cancer, regardless of its utility.

III.A. Natural Food Constituents

11-A 21 U.S.C. § 342(a)(1).

11-B *Id*. (Emphasis added.) The focus of the second clause of § 402(a)(1) is on the manner in which a substance becomes part of food, i.e., its natural occurrence, not on its character. A substance is considered naturally occurring when it is an inherent constituent of a food marketed without processing even though it may be identical to compound synthesized in the laboratory. See Poisonous or Deleterious Substances in Food, 39 Fed. Reg. 42743, 42744 (1974). Similarly, the category of food additives is not confined to substances synthesized by man. An apple used in making applesauce would be a food additive if it were not generally recognized as safe, while a synthesized chemical preservative might be so well-tested that it would qualify as GRAS.

11-C The 1906 Act declared food adulterated "if it contains any *added* poisonous or other *added* deleterious ingredients which may render such article injurious to health. . . ." Federal Food and Drugs Act of 1906, § 7, 34 Stat. 768 (1906) (emphasis added). Most of the early bills to reform the law would have changed that language to define food as adulterated "if it bears or contains any poisonous or deleterious substance which may render it dangerous to health. . . ." S. 2000, § 3(a)(1) (introduced January 4, 1934), S. 2800, § 3(a)(1) (introduced February 6, 1934) and as revised March 15, 1934), S. 5, § 3(a)(1) (introduced January3, 1935), S. 5, § 301(a)(1) (reported in the House May 31, 1935), S. 5, § 11(a)(1) (introduced January 6, 1937). The language Congress ultimately adopted to deal specifically with naturally occurring adulterants appeared mysteriously in a bill prepared by a subcommittee of the

House Interstate and Foreign Commerce Committee and reported to the House on August 25, 1936 as a substitute for the bill (S. 5) passed by the Senate several months earlier. While the committee's report does not explain why this wording was added, the legislative record of the earlier bills may suggest an answer.

The earliest proposed bills had deleted the word "added" from the language of the 1906 Act to allow FDA to regulate any food that might be dangerous, whether the deleterious constituent occurred naturally or was put there by artifice. Proposed Federal Food, Drug and Cosmetics Act: Hearing on S. 2800 Before the Senate Committee on Commerce, 73rd Cong., 2d Sess. (1934). The bills also substituted the word "dangerous" for "injurious." FDA Chief Walter G. Campbell pointed out to both House and Senate committees that during Congressional consideration of the 1906 Act, language that would have prohibited interstate transportation of any food naturally containing an "injurious" substance had been deleted because of concern that it would outlaw foods such as coffee and tea. Thus, the 1906 Act had been limited to foods containing added adulterants. But, Mr. Campbell explained, the 1906 Act also left such foods as poisonous mushrooms and particularly toxic varieties of West Coast mussels, which acquire their injurious properties naturally, beyond effective federal control. The word "dangerous" was therefore applied to foods naturally containing poisonous or deleterious substances in order to differentiate "between those products which may be injurious to health in a mild way and those that are unquestionably dangerous to health in a very definite way." Proposed Federal Food, Drug and Cosmetics Act: Hearings on S.5 Before the Senate Committee on Commerce, 74th Cong., 1st Sess. (1935); Hearings Before the House Committee on Interstate and Foreign Commerce, 74th Cong., 1st Sess. 1935).

The final wording of § 402(a)(1) returned to the word "injurious," but omi-ted "added" from the second clause--in order to reach naturally occurring poisons. Although not spelled out in the legislative history, the rationale of the final language may be inferred. "Injurious" had been the standard for all FDA enforcement actions under the 1906 Act, and Congress was reluctant to change language which had already been interpreted by the courts. But to prevent draconian enforcement against foods that naturally contained a deleterious substance, the House Committee added the proviso requiring the Government to prove that a substance was harmful when consumed in ordinary quantities. In other words, the phrase appears to have been another means of differentiating between "mildly" disturbing and "unquestionably" dangerous non-asded substances without abandoning the familiar term, "injurious." Statements during hearings indicate foods such as coffee, tea rhubarb (which naturally contains oxalic acid), cocoa, and similar foods were not to be regulated. Congress wanted to reach only foods such as the poisonous mushrooms, mussels, and "Burma beans" that FDA witnesses had cited as examples of foods that are highly toxic in their natural state.

12-A 43 F. Supp. 749 (N.D. Mo. 1942).

12-B 43 F. Supp. at 750.

12-C 43 F. Supp. at 751.

13-A See supra note 11-C. In Certified Color Industry v. Folsom, 236 F.2d 886 (2d Cir. 1956), the court discerned in the legislative history of § 402(a)(1) a rough balancing of risks and benefits. The court pointed out that in § 402(a)(1) Congress had differentiated between added and naturally occurring poisonous substances, precluding a finding of adulteration unless a naturally occurring substance was present in sufficient quantity to ordinarily render the food routinely injurious when ingested in the customary fashion.

13-AA There is no other satisfactory basis for explaining the agency's understandable silence on the subject of nitrates as natural constituents of many green vegetables. See generally Congressional Research Service, Nitrate Food Contamination: A Case Study (August 31, 1978).

13-B See 21 C.F.R. Part 189. It has attempted to impose similar limitations on the use of specific ingredients in drugs and cosmetics. An example is chloroform, which the agency banned from use in cosmetics based on a finding by the National Cancer Institute that the substance induces cancer in laboratory animals. The agency relied on § 601(a) of the Act, 21 U.S.C. 361(a), whose language parallels the first clause of § 402(a)(1). In so doing, however, the agency purported to evaluate whether the risk was outweighed by any benefit. See Chloroform as an Ingredient of Human Drug and Cosmetic Products, 41 Fed. Reg. 26842 (1976).

14-A See Public Citizen, Inc. v. Schmidt, [1977] Food Drug Cos. L. Rep. (CCH) ¶ 70,171.13 (D.D.C. 1976).

15-A *See* *Poisonous Or Deleterious Substances in Food*, 39 Fed. Reg. 42743 (1974).

15-B Hutt, *The Basis and Purpose of Government Regulation of Adulteration and Misbranding of Food*, 33 Food Drug Cosmetic Law J. 505, 533-534 (1978). *See* Hutt, *Unresolved Issues in the Conflict Between Individual Freedom and Government Control of Food Safety*, 33 Food Drug Cosmetic Law J. 505, 585-587 (1978).

15-CC Polychlorinated Biphenyls (PCB's), 42 Fed. Reg. 17487 (1977); Aflatoxins in Shelled Peanuts and Peanut Products Used as Human Foods, 39 Fed. Reg. 42748 (1974).

15-C Such contaminants could fit the Act's broad definition of "food additive," 21 U.S.C. § 321(S), although there is little in the legislative history to suggest this is a result Congress contemplated and some evidence to the contrary. The House Commerce Committee report on the 1958 Food Additives Amendment stated that "accidental" additives were not included in the terms of the legislation.

> The principal examples of both intentional and incidental additives are substances intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting or holding food.
>
> On the other hand, substances which may accidentally get into a food, as for example, paints or cleaning solutions used in food processing plants, are not covered by the legislation. These additives are generally referred to as "accidental additives," since these substances if properly used may not reasonably be expected to become a component of a food or otherwise to affect the characteristics of a food. If accidental additives do get into food, the provisions of the Food, Drug, and Cosmetic Act dealing with poisonous and deleterious substances would be applicable.

H. R. Rep. No. 2284, 85th Cong., 2d Sess., 3-4 (1958).

15-D 21 U.S.C. § 342(a)(1).

16-A 21 U.S.C. § 348(c)(4): see 39 Fed. Reg. 42744 (1974).

16-B The House Commerce Committee report on the Food Additives Amendment states:

> The legislation covers substances which are added intentionally to food . . . [and] substances which may reasonably be expected to become a component of any food or to affect the characteristics of any food.

H.R. Rep. No. 2284, 85th Cong., 2d Sess. 3 (1958). See also statement quoted in note 15-C supra.

16-C See Poison or Deleterious Substances in Food, 39 Fed. Reg. 42743 (1974).

17-A 21 U.S.C. § 342(a)(1).

17-B There is little discussion in the legislative history about the application of § 402(a)(1) to "added" substances. Congress' main concern in its consideration of this section focused on language designed to reach naturally occurring dangerous substances. See note 11-C, supra.

17-C Federal Food, Drug and Cosmetic Act of 1938, Pub. L. No. 75-717, § 402(a)(1), 52 Stat. 1046 (codified at 21 U.S.C. § 342(a)(1) (1976)); Food and Drug Act of 1906, Pub. L. No. 59-384, ch. 3915, § 7, 34 Stat. 768.

17-D 232 U.S. 399 (1914).

18-A 232 U.S. at 411. The Supreme Court has ruled that the language interpreted in Lexington Mill survived in the § 402(a)(1) test for adulteration. Flemming v. Florida Citrus Exchange, 358 U.S. 153, 161 (1958).

18-AA 232 U.S. at 412.

18-AB See Hearings on S. 2800 Before the Senate Comm. on Commerce, 73d Cong. 2d Sess. 530 (1934).

18-B D. Mass., May 22, 1945 (unreported).

18-C Id. as reported in Kleinfeld and Dunn, Federal Food, Drug and Cosmetic Act: Judicial and Administrative Record 1938-1949, 310, 313 (Food Law Institute Series, 1949).

19-A See Poisonous and Deleterious Substances in Food, 39 Fed. Reg. 42743 (1974), 42 Fed. Reg. 52814 (1977). The legislative history is compatible with this position. Testimony during hearings on the 1938 Act indicates that any substance that was not "normal" or "natural" to a food, or was added by "artifice" in manufacture, was considered to be "added." Hearings on S. 2800 Before the Senate Committee on Commerce, 73rd Cong., 2d Sess. (March, 1934). The courts have generally accepted this broad reading of "added." In United States v. 1,680,000 Pounds of White Corn, No. T-4173 (D. Ka. Dec. 18, 1970), the court found aflatoxin mold on corn to be an "added" substance because it is "not a natural constituent of corn." Similarly, in United States v. An Article of Food, etc., 395 F. Supp. 1184 (1975), the court agreed with FDA's contention that "the test for determining whether a substance is added is whether it occurs naturally in the food," citing House hearings preceding the 1938 Act to support this conclusion. In that case mercury in swordfish was held to be an "added" substance because it "is not naturally produced by the fish, but is acquired through its external food supply." 395 F. Supp. at 1186. But see U.S. v. Anderson Seafoods, Inc., 447 F. Supp. 1151 (D.C. Fla. 1978).

19-B Id. at 1155.

19-C It is true that in recent years FDA has sometimes undertaken to issue regulations defining a substance as an adulterant under section 402(a)(1) or announcing the quantity of a toxicant present in food that will trigger regulatory action under this standard--a so-called "action level." In this fashion the agency has attempted to reduce the burden of demonstrating a hazard in each individual enforcement proceeding. See *United States v. Ewig Bros*., 502 F.2d 715 (7th Cir. 1974). Compare *United States v. Anderson Seafood, Inc*., 447 F. Supp. 1151 (D. Fla. 1978).

III.B. Environmental Contaminants of Food

20-A 21 U.S.C. § 342(a)(2)(A).

20-B 21 U.S.C. § 346.

21-A 21 U.S.C. § 346.

21-B The legislative history suggests that two major concerns motivated Congress to modify the approach of the 1906 Act. While Congress recognized that some potentially deleterious ingredients in food were ubiquitous, it desired to enhance FDA control over consumer exposure to poisonous substances in food from all sources. Agency officials complained that the 1906 Act only allowed consideration of the health impact of an added poison in a single commodity. Congress wanted to allow FDA to take into consideration the extent to which consumers were exposed to a deleterious substance from other sources as well. Hearings on S. 1944 Before a Subcommittee on Commerce, 73rd Cong., 2d Sess. ____ (1933). FDA officials also complained about the burden imposed on the agency whenever it attempted to enforce the 1906 Act's prohibition against added poisonous substances. That law required a showing that the particular lot of food which was the subject of the enforcement proceeding contained enough added poison to present a genuine risk to health. In each case the government had to summon outstanding toxicologists to testify that the quantity of added poison in the food was harmful. This procedure was cumbersome, expensive, and unpredictable. Hearings on S. 2800 Before the Senate Committee on Commerce, 73rd Cong., 2d Sess. ____ (1934).

The means Congress chose to remedy these drawbacks was to simply declare a food to be adulterated, and thus subject to enforcement under § 402(a)(2), if it contained any added poisonous or deleterious substance. The quantity of the substance and the extent to which the food might be harmful were immaterial. The agency would only have to prove that the substance was poisonous and that it was "added." It could then set tolerances for those substances that were important or unavoidable in food production.

21-C Legislative history regarding what substances would qualify for the "required" or "unavoidable" exceptions--and thus be eligible for tolerances--is again scanty. A Senate Report described these exceptions by example, noting that "poisonous sprays for fruits and vegetables to protect them against insects or fungus diseases" might be required for production and that unavoidable contaminants might be tolerated "where purification process[es] cannot entirely eliminate a contaminant of raw materials, or where some contaminant is unavoidably introduced in factory operations." S. Rep. No. 646, 74th Cong., 1st Sess. ____ (1935). Congress obviously was principally concerned about pesticide residues on raw agricultural commodities. Throughout the hearings and floor debates representatives of apple-producing states expressed fear that FDA would prescribe excessively stringent tolerances. See, e.g., 79 Cong. Rec. 4848 (1935); 83 Cong. Rec. 7783-86, 7894-98 (1938). FDA's Campbell made clear that pesticide residues would fall within the tolerance-setting authority because they were required in food production. He asserted that many pesticides were "regarded as absolutely essential in the production of our supply of fruits and vegetables." Hearings on S. 5 Before A Subcommittee of the House Committee on Interstate and Foreign Commerce, 74th Cong., 1st Sess. ____ (1935).

Nothing in the legislative history reveals what other substances might be eligible for tolerances. The other examples of "added" poisonous substances that FDA wanted authority to control included items that were not required for production or that could be avoided by good manufacturing practice, such as the contamination of sugar with arsenic from smoke blowing in through open windows. Id. However, when pointedly asked whether or not the authority to establish tolerances was chiefly directed at residues of pesticide sprays, Campbell replied:

> "Not at all. . . . They are not alone. There are a great many products in which added deleterious substances may be found. They are being discovered every day. We never know where we are going to find them. They may be found where least suspected, due, sometimes, to careless manufacturing operations, such as using lead manufacturing equipment, and such as the deliberate addition of ethylene glycol to frozen eggs. . . ." Hearings on S. 1944 Before A Subcommittee of the Senate Committee on Commerce, 73rd Cong., 2d Sess. ____ (1933).

21-D Poisonous or Deleterious Substances In Food: Notice of Proposed Rule Making, 39 Fed. Reg. 42743, 42745 (1974).

21-E Id. On a casual reading, §§ 402(a)(1) and (2)(2)(A) of the Act appear redundant. Section 402(a)(1) provides that an added poison will adulterate food only if it is present in quantities that may pose a risk to health. It contemplates that FDA must establish the requisite degree of danger for any food by evidence in court. By contrast, § 402(a)(2)(A), read in conjunction with § 406, appears to prohibit the addition to food of any poisonous substance--regardless of the quantity or the degree of risk the substance poses. To establish that a food is adulterated under § 402(a)(2)(A), FDA need only prove that the substance is added and that it is capable of producing toxic effects. Section 406 authorizes FDA to relax this unequivocal prohibition for a substance that cannot be avoided by good manufacturing practice that is necessary in the production of a food. Together these latter two provisions appear to create a system requiring FDA "licensure" or approval--in the form of a tolerance--for any added poison.

It is puzzling why Congress retained the first clause of § 402(a)(1) when in §§ 402(a)(2)(A) and 406 it created a more comprehensive system for regulating added food constituents. The legislative history of the 1938 Act does not resolve the puzzle, although it suggests a possible explanation for what, in retrospect, seems an oversight. Until final House passage, § 402(a)(1) did not differentiate between added and naturally occurring substances; it declared a food adulterated if it contained any poisonous or deleterious substance that might render it "dangerous to health. One objective of the new legislation was to enable FDA to regulate foods whose natural constituents posed a risk to health. Since earlier versions of the bill contained a provision similar to § 402(a)(2), which dealt explicitly with added substances, it would have been possible, perhaps natural, to read earlier versions of § 402(a)(1) as applying only to naturally occurring poisons. However, when the House added the second clause of § 402(a)(1)--establishing the "ordinarily injurious" standard for naturally occurring poisons--it thereby raised an inference that the first clause applied to added substances.

The result of this legislative handiwork is that FDA may in theory proceed on either of two bases against a food that contains an added poisonous substance--under the "may render injurious" standard of § 402(a)(1) or under § 402(a)(2)(A), which prohibits any added poison for which no tolerance has been set. The agency has usually relied only on § 402(a)(1). At first blush, it is difficult to see why FDA would ever invoke this section, which appears to impose on it a heavier burden of proof. Perhaps it has wanted to avoid having to explain why, in the face of the word "shall" in § 406, it had not established a single tolerance for an unavoidable or necessary added poisonous substance. In addition, agency enforcement personnel may have quickly concluded, since most seizures are not contested, that it was as easy to make a case based on § 402(a)(1), and reliance on this provision did not call into question its administrative authority. Until the late 1960's, FDA relied almost exclusively on court enforcement and never fully explored the range of administrative powers open to it.

21-F 21 U.S.C. § 348a.

21-G Though FDA never invoked its formal authority, § 406 theoretically remained an important part of the agency's statutory armament, for § 408 did not deal with the problems of pesticide drift or persistence, which result in the contamination of foods on which no pesticide is used or intended to remain. Furthermore, prior to 1958, when the Food Additives Amendment was passed, without section 406 the statute would have afforded FDA no basis, other than section 402(a)(1), to deal with the occurrence of pesticides residues in processed food at levels above the tolerance established for the raw commodity.

21-H It should be noted that § 406 does not enable FDA to control the occurrence of contamination. To the extent that environmental contaminants of food are unavoidable, as is the case with mercury in swordfish, establishment of a tolerance can have no effect on the levels that occur in the environment. What a § 406 tolerance does, in theory, is limit human exposure to the contaminant by eliminating food containing higher levels from the food supply.

22-A Poisonous or Deleterious Substances in Food: Notice of Proposed Rule Making, 39 Fed. Reg. 42743, 42744 (1974).

22-B Id. See also Alfatoxins in Shelled Peanuts and Peanut Products Used As Human Food: Proposed Tolerance, 39 Fed. Reg. 42748 (1974).

22-BB I have previously adverted to the potential flexibility of these requirements, and to FDA's solicitude for familiar constituents of the food supply. See text accompanying note ____ supra.

22-C 21 U.S.C. § 346.

22-D Once a tolerance has been established, a food that contains the contaminant in concentrations that exceed the tolerance is unlawful without further inquiry into the health hazard it may pose. See 21 U.S.C. §§ 342(a)(2)(A), 346.

22-E Poisonous or Deleterious Substances: Final Rule, 42 Fed. Reg. 52814, 52816 (1977). See also Letter from Donald Kennedy, Commissioner of Food and Drugs, to J. B. Cordaro, Group Manager, Food Group, Office of Technology Assessment (Jan. 22, 1979).

23-A In 1974, when FDA was first confronted with the need to determine the marketability of PBB-contaminated foods produced in Michigan, it initially established its "action level" (a form of "tentative" tolerance, see note ____ infra, and accompanying text) at the level measurable by the best available analytical methods. Testimony of Dr. Albert Kolbye at Hearings on Polybrominated Biphenyls in Lansing, Michigan (May 29, 1975).

23-B 21 U.S.C. § 701(e). See Hamilton, Rulemaking on a Record by the Food and Drug Administration, 50 Tex. L. Rev. 1132 (1972).

23-C 21 U.S.C. § 701(e)( ). A tolerance that is stayed by objections and request for a hearing serves as an "action level" for FDA enforcement during the pendency of the hearing. See note ____ infra, and accompanying text. See also Poisonous or Deleterious Substances: Final Rule, 42 Fed. Reg. 52814, 52818 (1977).

23-D See 21 U.S.C. § 701(f).

24-A See Poisonous or Deleterious Substances: Final Rule, 42 Fed. Reg. 52814, 52819 (1977) (to be codified in 21 C.F.R. § 109.4(b); Poisonous or Deleterious Substances in Food: Notice of Proposed Rule Making, 39 Fed. Reg. 42743, 42745 (1974).

24-BC For example, in the case of aflatoxin contamination of corn, a United States District Court in Georgia refused to enjoin a distributor of grain from shipping corn containing a quantity of aflatoxin in excess of the FDA's informal action level of 20 ppb. United States v. Boston Farm Center, ___ F. Supp. ___, No. 77-42 (M.D. Ga. Dec. 7, 1977). Instead of accepting FDA's determination that the presence of 20 ppb aflatoxin rendered the corn injurious to health, the District Court examined the evidence presented and concluded that aflatoxin-contaminated corn was not injurious to health unless the quantity of aflatoxin present exceeded 100 ppb.

24-C See Poisonous or Deleterious Substances: Final Rule, 42 Fed. Reg. 52814, 52817 (1977); Poisonous or Deleterious Substances in Food: Notice of Proposed Rule Making, 39 Fed. Reg. 42743, 42745 (1974).

24-D See, e.g., Letter from Donald Kennedy, Commissioner of Food and Drug Administration, to Congressman William M. Brodhead (Aug. 12, 1977) (Denying Petition to Lower Action Levels for Polybrominated Biphenyls).

24-E Poisonous or Deleterious Substances: Final Rule, 42 Fed. Reg. 52814, 52819 (1977) (to be codified in 21 C.F.R. § 109. 4(b)). This procedure represents a retreat from the agency's original proposal, which would have provided notice-and-comment rulemaking for the establishment of action levels, with one important difference: any "proposed" action level would be enforced in the interim. Poisonous or Deleterious Substances in Food: Notice of Proposed Rule Making, 39 Fed. Reg. 42743, 42746 (1974). Under the procedure finally adopted, FDA's action levels will not be the product of a public proceeding, and may therefore carry less weight in court enforcement actions. See note 24-BC, supra.

25-A 21 U.S.C. § 321(s).

26-A Id. Emphasis added.

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III.C Intentional Ingredients in Processed Foods

25-A 21 U.S.C. § 321(s).

26-A *Id.* (Emphasis added.)

26-B Section 402(a)(2)(C) declares a food adulterated "if it is, or it bears or contains, any food additive which is unsafe within the meaning of section 409 . . ." 21 U.S.C. § 342(a)(2)(C). Section 409(a) provides in relevant part:

> A food additive shall, with respect to any particular use or intended use of such additives, be deemed to be unsafe for the purposes of the application of clause (2)(C) of section 402(a), unless-- . . .
>
> > (2) there is in effect, and it and its use or intended use are in conformity with, a regulation issued under this section prescribing the conditions under which such additive may be safely used.
>
> While such a regulation relating to a food additive is in effect, a food shall not, by reason of bearing or containing such an additive in accordance with the regulation, be considered adulterated within the meaning of clause (1) of section 402(a).

26-C 21 U.S.C. § 348(c)(3)(A). See generally Freedman, *Reasonable Certainty of No Harm: Reviving the Safety Standard for Food Additives, Color Additives, and Animal Drugs*, 7 Ecology L.Q. 245 (1978).

26-D 21 U.S.C. § 348(c)(3)(A). Neither the Delaney Clause nor any other provision of section 409 specifically mandates that FDA shall withdraw approval of an approved additive subsequently found to induce cancer or to be otherwise unsafe, but this seems an unmistakable inference from the previous governing initial approval of food additives. FDA has historically assumed that a clear finding of carcinogenicity ordinarily requires prompt action to terminate approval of an additive. *But see* Culliton and Waterfall, *Nitrites--to ban or not to ban*, 1978 Brit. Med. J. 1613.

26-E This standard is implicit in the requirement of section 408(b)(2)(C) that a food additive petition contain "all relevant date on the physical or other technical effect such additive is intended to produce. . . ." 21 U.S.C. § 348(b)(2)(G).

27-A See Saccharin And Its Salts, 42 Fed. Reg. 19995, 20002 (1977); Freedman, supra note 26-C,

27-B Both the House and Senate reports stated:

> The question of whether an additive produces such effect (or how much of an additive is required for such effect) is a factual one, and does not involve any judgment on the part of the Secretary of whether such effect results in any added "value" to the consumer of such food or enhances the marketability from a merchandising point of view.

H.R. Rep. No. 2284, 85th Cong., 2d Sess. 6 (1958); S. Rep. No. 2422, 85th Cong., 2d Sess. 7 (1958).

27-C 21 U.S.C. § 348(c)(1)(A) specifies:

> The Secretary shall--
>
> (A) by order establish a regulation (whether or not in accord with that proposed by the petitioner) prescribing, with respect to one or more proposed uses of the food additive involved, the conditions under which such additive may be safely used (including, but not limited to, specifications as to the particular food or classes of food in or on which such additive may be used, the maximum quantity which may be used or permitted to remain in or on such food, the manner in which such additive may be added to or used in or on such food, and any directions or other labeling or packaging requirements for such additive deemed necessary by him to assure the safety of such use), and shall notify the petitioner of such order and the reasons for such action; or
>
> (B) by order deny the petition, and shall notify the petitioner of such order and of the reasons for such action.

27-D Authority to do is less obvious from the language of § 409(c)(1)(A), but has been exercised occasionally. See, e.g., Saccharin and its Salts, 42 Fed. Reg. 19995 (1977); Aspartame, 39 Fed. Reg. 27317 (1974). (FDA's approval of aspartame, another artificial sweetener, has since been stayed. 40 Fed. Reg. 56907 (1975)).

27-E 21 U.S.C. § 348(c)(1)(A).

27-F E.g., BHA, 21 C.F.R. § 172.110(c) (1978); Sodium nitrite, 21 C.F.R. § 172.175(b) (1978); Potassium iodide, 21 C.F.R. § 172.375(b) (1978); Aspartame, 39 Fed. Reg. 273.7 (1974).

27-G See 21 U.S.C. § 348(b).

27-H A petitioner can ascertain these standards by asking the agency's Division of Food and Color Additives, but they are not set forth in detail in the Code of Federal Regulations or any other agency publication. 21 C.F.R. § 170.20(a) (1978) merely states:

> In reaching a decision on any petition filed under section 409 of the act, the Commissioner will give full consideration to the . . . adequacy of the methods employed to demonstrate safety for the proposed use, and the Commissioner will be guided by the principles and procedures for establishing the safety of food additives state in current publications of the National Academy of Sciences-National Research Council. . . .

The regulations governing the form and content of food additive petitions are brief and general. See 21 C.F.R. §§ 170.20, .22, Part 171.

27-I Letter to the author from Joseph Rodricks, Ph.D., Assistant to the Director for Science Policy, Bureau of Foods, U.S. Food and Drug Administration, September 28, 1978. There remains some uncertainty about the extent to which FDA routinely requires long-term testing for direct food additives, and there apparently have been exceptions to the generalization set forth in the text. A deficiency in the agency's administration of section 409 has been its failure to spell out, in regulations or some other formal policy statement, precisely what tests it regularly requires.

27-J See 21 U.S.C. § 348(8); 21 C.F.R. § 170.17.

28-X In 1976 FDA was sharply criticized by the General Accounting Office for allowing saccharin to be used at levels corresponding to 1/30 of the "no observed effect" dose in animals. The agency acknowledged that this represented a departure from its standard practice. Report of the Comptroller General of the United States, Need to Resolve Safety Questions of Saccharin 27 (Aug. 16, 1976).

28-A 21 C.F.R. § 170.22; Rodricks letter, supra note 27-I.

28-B Conversation with Joseph Rodricks, Ph.D., March, 1977 (see supra note 27-I).

28-C Saccharin and its salts, supra note 27-A at 19998; see Page, Chronic Toxicity and Carcinogenicity Guidelines, 1 J. of Envt'l Pathology and Toxicology 161, 177-78 (1977); Doniger, Federal Regulation of Vinyl Chloride: A Short Cause in the Law and Policy of Toxic Substances Control, 7 Ecology L.R. 497, 512-513 (1978) (and sources cited therein).

28-D The principal difficulty encountered in determining the risk posed by an environmental contaminant of food, or any other constituent for advance FDA approval need not be obtained, is the shortage of reliable safety data. No "petitioner" need seek permission to market swordfish containing mercury, and thus the burden of assembling data and, in some cases, conducting needed additional tests falls on the government, often on FDA or state agencies. Letter from Donald Kennedy, Commissioner of Food and Drugs, to J.B. Condaro, Office of Technology Assessment, January 22, 1979; conversation with Robert S. Jackson, M.D., Assistant State Health Commissioner, Director, Office of Health Protection and Environmental Management, Virginia Department of Health, October 22, 1978; Letter to the author from Joseph V. Rodricks, Assistant to the Director, Bureau of Foods, U.S. Food and Drug Administration, September 28, 1978.

29-A See text accompanying notes 23-B - 24-A; letter from Donald Kennedy, Commissioner of Food and Drugs, supra note 28-D.

29-B 21 U.S.C. §§ 348(b)(5), (c)(1)-(2); see 21 C.F.R. §§ 171.1(i)(2), 171.100.

29-Ba [Need to confirm with Pape or Rodricks.]

29-C 21 U.S.C. § 348(f); 21 C.F.R. § 171.110. FDA has construed "person adversely affected" to embrace opponents of the approval of an additive which the Commissioner has concluded is safe, as well as manufacturers or users of additives whose petitions are turned down. See, aspartame, 39 Fed. Reg. 27317 (1974); 40 Fed. Reg. 56907 (1975). Food Chemical News reports that, "FDA-ers now believe the Board of Inquiry on Aspartame probably will not begin until spring and may be delayed until summer." "All UAREP Documents on Aspartame to be Submitted to FDA," 20 Food Chemical News 36 (1978).

29-D 21 U.S.C. § 348(e). More than a year elapsed between FDA's initial approval of Aspartame, 39 Fed. Reg. 27317 (1974), and its decision to stay the effect of the food additive regulation. 40 Fed. Reg. 56907 (1975). During that time, the successful petitioner was technically free to market the additive even though the agency had agreed to grant a formal hearing on its decision. For practical and public relation reasons, the firm chose not to do so.

29-E 21 U.S.C. § 348(g).

29-F When FDA issues a regulation on its own initiative, e.g., when the agency is seeking withdraw approval to ban an additive, the Act requires that at least 30 days expire between initial publication and issuance of a final order. No such requirement applies to a regulation issued in response to a food additive petition.

21 U.S.C. § 348(d). See Saccharin and Its Salts, supra note 27-A.

29-X Both are petitions for the approval of artificial sweeteners, cyclamate and aspartame. Cyclamate was banned as an ingredient in food in 1969, following FDA's receipt of evidence suggesting that it might be an animal carcinogen. The sweetener not previously been regulated as a food additive, but rather was being used -- with FDA concurrence -- on the premise that it was GRAS. The new evidence destroyed its reputation as safe, thus requiring the manufacturer to obtain approval of a food additive petition before the sweetener could lawfully be used again. In 1973, such petition was submitted, and in 1976 FDA Commissioner Alexander M. Schmidt declined to approve it on the ground that doubts about its carcinogenicity had not been resolved. 41 Fed. Reg. 43754 (1976). The manufacturer, Abbott Laboratories, demanded and received a formal evidentiary hearing. Its interest in pursuing the matter through the full administrative process was probably influenced by FDA's announcement in April 1977 that it intended to ban the use of saccharin, the only artificial sweetener currently approved for use in this country.

The second proceeding under section 409 that has resulted in a request for a hearing involves aspartame, a new sweetener that appeared to be an alternative to both cyclamate and saccharin. FDA approved the food additive petition for Aspartame in 1974. 39 Fed. Reg. 27317 (1974). Its action provoked formal objections and a request for a hearing from an attorney associated with the consumer movement and a member of a distinguished medical faculty, both of whom contended that the agency had misinterpreted data showing that the ingredient could cause brain damage in infants and children. FDA agreed that a hearing was justified, and subsequently persuaded the affected parties to submit the dispute to a Public Board of Inquiry, a tribunal provided for by agency regulations and resembling some conceptions of a "science court." 21 C.F.R. Part 15. The hearing on Aspartame is expected to occur in 1979.

29-G 21 U.S.C. § 321(5).

30-A *See* *Food Additives: Hearings on Bills to Amend the Federal Food, Drug, and Cosmetic Act with Respect to Chemical Additives in Food Before the Subcomm. on Health and Science of the House Comm. on Interstate and Foreign Commerce*, 85th Cong., 1st & 2d Sess. 442, 460-65 (1957-1958) (Statement of George P. Larrick, Commissioner of Food and Drugs).

30-B As the cyclamate experience demonstrates, GRAS status affords no protection for an ingredient comparable to that customarily provided by a "grandfather clause," which usually permanently exempts existing activities or marketed products from new statutory requirements. *See* Cyclamic Acid and Its Salts, 34 Fed. Reg. 17063 (1969).

30-C Most of these decisions, it should be noted, have involved drugs intended for use in humans or in animals. The Act requires premarket proof of safety and effectiveness for any "new" human or animal drug, see 21 U.S.C. §§ 355, 360b, and defines a "new drug" as one whose safety or effectiveness is not "generally recognized by qualified experts." 21 U.S.C. § 321(p), (w). Accordingly, many of the decisions interpreting the criteria for premarket approval of drugs are relevant to interpreting the criteria for GRAS status. Moreover, several of the pertinent drug decisions involve drugs intended for use in food producing animals, which may become components of human food. *See*, *e.g*. United States v. Articles of Food & Drug, Coli-Trol 80 Medicated, 372 F. Supp. 915 (N.D. Ga. 1974), aff'd, 518 F.2d 743 (5th Cir. 1975); United States v. 1,048,000 capsules . . ., 347 F. Supp. 768 (S.D. Tex. 1972), aff'd, 494 F.2d 1158 (5th Cir. 1974).

30-D See United States v. Naremco, Inc., 553 F.2d 1138 (8th Cir. 1977).

30-E For an ingredient to be eligible for GRAS status under this leg of the exception, FDA requires essentially the same quantity and quality of scientific evidence as would be needed to support approval of a food additive. 21 C.F.R. § 170.30(b).

30-F United States v. Articles of Drug Labeled "Quick-o-ver," 274 F. Supp. 443 (D. Md. 1967). FDA's regulations state that:

> (a) General recognition of safety may be based only on the views of experts qualified by scientific training and experience to evaluate the safety of substances directly or indirectly added to food. The basis of such views may be either (1) scientific procedures or (2) in the case of a substance used in food prior to January 1, 1958, through experience based on common use in food. General recognition of safety requires common knowledge about the substance throughout the scientific community knowledgeable about the safety of substances directly or indirectly added to food.

21 C.F.R. § 170.30(a) (1978).

30-G 21 C.F.R. § 170.30(b):

> General recognition of safety based upon scientific procedures shall require the same quantity and quality as is required to obtain approval of a food additive regulation for the ingredient. General recognition of safety through scientific procedures shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data and information.

31-A A conclusion that an ingredient is not GRAS may, however, interrupt its use, for a food additive may not lawfully be used until FDA has issued a regulation approving its use -- a process that can require several months or longer. FDA has devised a system of "interim food additive regulations" to bridge this gap where it concludes that sudden suspension of use would not be appropriate. See note 32-A infra and accompanying text.

31-B 21 C.F.R. § 170.30(h).

31-C See, e.g., 21 C.F.R. § 182,1180 (caffeine); § 182.1440 (magnesium stearate); § 182.1295 (ethyl formate).

31-D See Substances Added Directly to Human Food Affirmed as Generally Recognized As Safe (GRAS), 21 C.F.R. § 184.1(f) (1978); See e.g., Sorbitol, 21 C.F.R. § 184.1835(e) (1978).

31-E Any intentional food ingredient found to cause cancer in humans would be banned by FDA as a matter of course, whether it was GRAS, prior sanctioned, or a food additive. The circumstance that is more likely to confront FDA with increasing frequency, however, is the discovery that a food ingredient is an animal carcinogen, as in the case of saccharin.

31-F 21 C.F.R. § 121.101(d)(4) (1969); Cyclamate and its Salts, supra note 30-B.

31-G 34 Fed. Reg. 17063 (1969). See Plotkin, The Cyclamate Ban: Science, Politics, and Law (April, 1978) (unpublished paper).

The conclusion suggested by the text is not dictated by the language of the statute, which does not specify whether the benefits of an ingredient can be weighed to determining whether it is GRAS. It could be argued that Congress' creation of the GRAS category reflects a recognition of the utility of commonly used food ingredients, and that the agency should consider such utility whenever new information respecting the risks posed by a familiar ingredient comes to light. A possible candidate for such an analysis might be sodium nitrite, widely used in preparing cured meat products whose benefits include preservation against botulism. Surely in such a case, one might argue, FDA should be able to consider such benefits, i.e., seek to avoid the ostensibly greater risk of botulism, in deciding whether or not to subject the ingredient to the rigorous standards of section 409(c).

This approach has never been formally espoused to FDA, but it is hinted at in one FDA proposal, though not in a context that involved a potential carcinogen. See General Recognition of Safety and Prior Sanctions for Food Ingredients, 39 Fed. Reg. 34194 (1974). Its formal adoption at this late date would be very difficult to explain, and would have the result of transforming the GRAS exception into a genuine grandfather clause, subject to forfeiture upon the agency's finding that the benefits of an ingredient did not justify an exception to the requirements of section 409(c). Moreover, in determining whether the Delaney Clause should apply, there is no valid scientific basis for distinguishing between food additives, which require formal FDA approval, and GRAS ingredients. As a group, GRAS ingredients may be less likely to be carcinogenic, simply because of their record of safe usage. The lack of evidence of adverse effects may also be a sufficient basis for assigning them a low priority for safety evaluation. But the health risks posed by a food constituent that is shown to induce cancer in experimental animals does not depend on the regulatory category into which it falls. See, Hutt,

32-A The Act makes no provision for the transition between loss of GRAS status and approval as a food additive. To bridge this gap, FDA has established procedures for the issuance of interim food additive regulations. 21 C.F.R. Part 180. An interim food additive regulation may be issued for an ingredient whose safety is brought into question by new evidence but whose continued use, pending the conduct of the studies necessary to resolve the safety issue, is found to pose no significant risk to human health. Since controversy about its carcinogenicity arose in the early 1970's, saccharin has been protected by an interim food additive regulation, as are mannitol and brominated vegetable oil (BVO). 21 C.F.R. §§ 180.25, 180.30, 180.37. See Freedman, supra note 27-A at 259-264. The interim regulation for BVO was attacked as beyond the agency's authority; and upheld, in Jacobsen v. Edwards, Food Drug Cos. L. Rep. (CCH) ¶ 56,059.10 (D.D.C. 1971), aff'd (D.C. Cir. 1972).

32-B Now codified at 21 C.F.R. § 182 § 182 (1978). The original list was initially proposed at 23 Fed. Reg. 9511 (1958).

32-C See General Recognition of Safety and Prior Sanctions for Food Ingredients, 41 Fed. Reg. 53600, 53603-4 (1976).

32-D See United States v. Naremco, Inc., 553 F.2d 1138 (8th Cir. 1977); United States v. Narenco, Inc., 420 F.2d 1126 (5th Cir. 1970).

32-E The Acting FDA Commissioner observed in 1977 that there are about 2,100 approved direct food additives and went on to describe the remainder of the universe of food ingredients and other constituents:

> There are over 400 nonflavor GRAS substances; approximately 1,650 flavors and spices, some of which are GRAS and some regulated additives; about 400 regulated direct food additives and on the order of 10,000 GRAS and regulated indirect additives. Additionally, there are some 65 regulated and 52 "provisionally listed" color additives. . . .

Food Additives: Competitive, Regulatory, and Safety Problems: Hearings Before the Senate Select Committee on Small Business, 95th

Cong., 1st Sess., Part 1, 44, 52 (1977) (Statement of Sherwin Gardner). See 21 C.F.R. § 181 (1978). The agency derives its estimates of overall exposure from a variety of sources, including USDA records of food sales and surveys conducted by the National Academy of Sciences/National Research Council.

33-A See 21 C.F.R. § 170.30(e), § 170.35, and Part 184. The objective of this program is eventually to produce a single, comprehensive list of ingredients which have been affirmed as GRAS based on current toxicological criteria, and whose continued use can be subjected to the conditions specified in the agency's affirming regulation. It should be noted, however, that the GRAS review embraces only those substances that appear on FDA's GRAS list, and that the agency has not been able to devise a procedure for forcing users of unlisted ingredients to seek review and confirmation of their safety.

33-C Poultry Products Inspection Act, Pub. L. No. 85-172, § 2, 71 Stat. 441 (1957) (codified at 21 U.S.C. §§ 451-469 (1976)). The date of passage of this Act, August 28, 1957, fell so near the enactment of the Food Additives Amendment very few substances qualify for exemption under its provisions. See Nitrates and Nitrites in Poultry Products, 42 Fed. Reg. 44376 (1977).

33-D Meat Inspection Act of March 4, 1907, ch. 2907, 34 Stat. 1260 (codified in scattered sections of Titles 5, 7, 16, 21, 43 U.S.C.).

33-E 21 U.S.C. § 321(t)(4).

33-X It is, however, a limited exemption. So-called "prior sanctioned" ingredients are excepted from the requirements for approval as food additives, but they are not exempt from the other food safety provisions of the Act, including § 402(a)(1). See 21 C.F.R. § 181 (1978).

33-Y For a discussion of FDA food standards of identity, see generally Merrill and Collier, "Like Mother Used to Make": An Analysis of FDA Food Standards of Identity, 74 Colum. L. Rev. (1974). In the mid-1950's approximately 50 percent of the foods purchased by American consumers were covered by standards of identity, which were designed primarily to preserve the economic integrity but were also employed by FDA to restrict the use of potentially toxic ingredients. See Atlas Powder Co. v. Ewing, 201 F.2d 347 (3d Cir. 1952), cert. denied 345 U.S. 923 (1953).

33-F See, e.g., 9 C.F.R. § 319.300 (1978); 9 C.F.R. § 381.169 (1978).

34-A Use of Sodium Nitrite, Sodium Nitrate, Potassium Nitrite, and Potassium Nitrate, 37 Fed. Reg. 23456 (1972).

34-B See Gardner, Sowbelly Blues, The Links Between Bacon and Cancer, Esquire, November, 1976, p. 112; Letter from Carol Foreman, Assistant Secretary for Food and Consumer Services, USDA to Donald Kennedy, Commissioner of Food and Drugs (April 22, 1977); Letter from Donald Kennedy to Carol Foreman (July 12, 1977). As interpreted by FDA, the "prior sanction" exception requires some evidence of official acquiescence, but such evidence can be very informal. No USDA regulations or FDA opinions employed the magic language "sanctioned." Prior sanctions have been based on actions ranging from a scientist's publication of an article acknowledging the safety of an ingredient to a USDA inspector's stamp of approval on processed meat to USDA's approval of labels bearing a statement of ingredients.

34-C Because of the diverse evidence of approval accepted by FDA, estimates of the number of ingredients that were sanctioned for one or more uses prior to 1958 are mere speculation, but persons familiar with the matter doubt the number exceeds 200. See 23 Fed. Reg. 9511 (1958); 24 Fed. Reg. 9368 (1959).

34-D Hutt, A Regulator's Viewpoint, in How Safe is Safe?, The Design of Policy on Drugs and Food Additives 116 (National Academy of Sciences 1974).

34-E There is no clear instances in which FDA has continued to approve the use of a prior sanctioned ingredient which itself has been found to induce cancer in experimental animals. The case most nearly on point is that of sodium nitrite, an ingredient used in the curing of many beef and most pork products, including notably bacon. Faced with a recent finding that sodium nitrite causes cancer in laboratory rats, FDA is considering proposing to terminate all its uses but allow a phase-out period. Smith Ever So Cautiously, the FDA Moves Toward a Ban on Nitrites, 201 Science 887 (1978).

34-F See 21 C.F.R. § 181.1(b). The rationale for the exception is not difficult to fathom. Congress presumably was aware of FDA's practice of responding to manufacturer inquiries about the safety of food ingredients, and was prepared to regard its responses as the functional equivalent of food additive approval. Furthermore, the special treatment accorded substances previously sanctioned by USDA can be explained in part by FDA's traditional deference to that department when it came to meat and poultry products, a deference that allowed Congress to treat such substances as USDA's concern.

35-A 21 C.F.R. § 181.5(b) (1978); Prior-sanctioned Food Ingredients, 38 Fed. Reg. 12737 (1973); Kingham, Statutory and Administrative Theories By Which FDA Avoids Applying the Delaney Clause 7 (Nov. 10, 1977) (unpublished paper on file with author). Cf. Sodium nitrite, supra note 34-A, in which FDA did not propose to ban certain uses of nitrites suspected of posing a carcinogenic risk because of its belief that those uses were prior sanctioned. FDA might have invoked § 402(a)(1) had it not been persuaded of the benefits of nitrite. Nothing in the legislative history of the Food Additives Amendment would suggest that Congress ever contemplated the possibility that a prior sanctioned ingredient might be found to be carcinogenic. Indeed Congress appears to have given no thought to the possibility that some prior sanctioned ingredients might later prove to be harmful in any way.

35-C See Sodium Nitrite, supra note 34-A; Nitrites in Poultry, supra note 33-C; General Recognition of Safety and Prior Sanctions for Food INgredients, 39 Fed. Reg. 34194 (1974). The only example cited by the agency of benefits that might legitimately be considered is the antibotulinal effect of sodium nitrite.

35-D In the case of a substance shown to induce cancer in laboratory animals, any opportunity to consider benefits of any kind depends on the substance's prior sanction status, which provides shelter against the Delaney Clause. FDA sometimes has discovered that its assumptions about the legal status of an ingredient were mistaken. Assistant Secretary Foreman's letter to FDA Commissioner Kennedy, see note supra, announcing that USDA had not in fact sanctioned sodium nitrite for use in poultry came as a surprise, and reflected a departure from that Department's informal historical position. Because evidence that sodium nitrite itself might induce cancer was then lacking, FDA was able to devise an interim solution that would permit limited continued use of the ingredient pending further scientific studies. See Nitrates and Nitrites in Poultry Products, 42 Fed. Reg. 44376 (1977). However, confirmation that sodium nitrite is a carcinogen should, under USDA's interpretation, automatically require termination of its use in poultry products even while the two agencies are struggling to construct a theory that will permit a phase-out of its use in beef and pork.

35-E Color Additives Amendments of 1960, Pub. L. No. 86-618, 74 Stat. 397 (codified in scattered sections of 21 U.S.C., principally § 376.)

36-A 21 U.S.C. § 321(t).

36-B 21 C.F.R. § 70.3(g). This regulation was not designed to subject food additives that impart color to regulation under the Color Additive Amendments, rather than under the Food Additives Amendment, although it has that effect. Rather, it was adopted as part of a since abandoned FDA scheme to subject certain cosmetic products to premarket clearnace. See Toilet Goods Mfgrs. Ass'n v. Finch, 419 F.2d 21 (2d Cir. 1969).

36-C A food containing a color additive that FDA has not approved is adulterated. 21 U.S.C. §§ 342(c), 376(a).

36-D 21 U.S.C. § 376(b)(4)(5), and (6); Freedman, supra note 27-A.

36-E 21 U.S.C. § 376(b)(7).

36-F 21 U.S.C. § 376(c). Such a requirement is not authorized for food additives.

36-G 21 U.S.C. § 376(b)(8).

37-A FDA has proposed to require label declaration of FD&C Yellow No. 5 when used to color foods and ingested drugs and to prohibit use in certain drugs for human use. This proposal is based on evidence that a substantial number of consumers suffer allergic-type reactions to the color. 42 Fed. Reg. 6835 (1977).

37-B 21 U.S.C. § 376(b)(5)(B), which reads in pertinent part as follows:

> A color additive (i) shall be deemed unsafe, and shall not be listed, for any use which will or may result in ingestion of all or part of such additive, if the additive is found by the Secretary to induce cancer when ingested by man or animal, or if it is found by the Secretary, after tests which are appropriate for the evaluation of the safety of additives for use in food, to induce cancer in man or animal, and (ii) shall be deemed unsafe, and shall not be listed, for any use which will not result in ingestion of any part of such additive, if, after tests which are appropriate for the evaluation of the safety of additives for such use, or after other relevant exposure of man or animal to such additive, it is found by the Secretary to induce cancer in man or animal.

37-C This statement requires qualification. Under § 706(b)(4), a color additive shall be deemed suitable and safe for use in food--and thus automatically eligible for listing--if FDA has published a finding that the substance is exempt from the definition of food additive because it is GRAS. This provision does not, however, exempt any color additive from the requirement of affirmative FDA approval.

37-X The obligation to be accurate demands a further qualification. As the next paragraph of the text explains, the Color Additives Amendments did authorize FDA to "provisionally list" colors then in use and believed to be safe, pending the completion of contemporary toxicological studies necessary to support full approval. Technically, the Delaney Clause does not apply to provisionally listed colors and it would, in theory, be possible to argue that FDA might lawfully authorize provisional listing--and continued use--of a carcinogenic color additive. But this argument would be even more fragile in this context than in the case of a once-GRAS food ingredient, see note ____ supra, for Delaney clearly would preclude permanent listing of such a color, and both the text and legislative history of the 1960 Amendments make clear that provisional listing was to be temporary for all colors. Moreover, FDA has made clear that it regards evidence of carcinogenicity as fatal to provisionally listed food colors. FD&C Red No. 2, 41 Fed. Reg. 5823 (1976); Certified Color Manufacturers Association v. Mathews, 543 F.2d 284 (D.C. Cir. 1976).

37-D Sodium nitrite has been used in curing poultry, to stabilize or "fix" color. Once USDA announced that sodium nitrite was not sanctioned for use prior to the 1958 Food Additives Amendment, FDA was faced with the difficult task of differentiating the uses of this substance as a food and color additive and determining the applicable statutory provisions for regulating its use. See 42 Fed. Reg. 44376 (1977).

37-E See Pub. L. 86-618, § 203, July 12, 1960. This section is not codified in the FD&C Act.

37-Y Prior to 1960, colors derived from coal tar dyes were subject to stringent regulation under § 406(b) of the original 1938 Act, a provision that has since been repealed. As FDA ultimately interpreted this provision, which required the agency to certify coal tar dyes shown to be "harmless," it forbade approval of any color that produced toxic effects at any dosage level in animal experiments--an extremely onerous standard. See Flemming v. Florida Citrus Exchange, 358 U.S. 153 rehearing denied, 358 U.S. 948 (1958). By contrast colors other than those derived from coal tar dyes were subject merely to the criteria of § 402(a)(1). The Color Additive Amendments were designed to both relax the stringency of the "harmless" standard to permit the use of coal tar colors shown to be safe at the levels proposed to be used, and to bring other colors under premarketing controls for the first time. See S. Rep. No. 795, 86th

Cong., 1st Sess. (1959); H.R. Rep. No. 1761, 86th Cong., 2d Sess. (1960).

37-XX This transitional authority conferred by the Color Additive Amendments was potentially open-ended in that Congress did not specify a final date by which all pre-1960 colors were either to be approved or terminated. Though Congress did prescribe an initial 2 and 1/2 year period, it also permitted FDA to extend this period by regulation when necessary to permit completion of requisite testing. This approach may be contrasted with Congress' approach in the 1958 Food Additives Amendment, which specified a two-year, non-extendable transitional period. However, the 1958 law also built into the food additive definition the exception for GRAS ingredients, which permitted FDA to postpone definitive evaluation of many "additives" for more than 30 years.

37-Z On at least one occasion, FDA restored a once-provisionally listed color to the list following a brief absence. The color was FD&C Red No. 4, once used by all producers of maraschino cherries. The agency deleted the color in 1966 following a controversial study that suggest it might cause teratogenic effects in dogs. It was persuaded to restore the color's provisional approval when cherry producers demonstrated how little of the substance consumers would be exposed to. In 1976 the agency once more terminated the provisional listing for Red No. 4 on the ground that the petitioners for its approval had never performed the toxicological tests necessary to resolve the earlier questions about its safety. 41 Fed. Reg. 41852, 41854 (1976).

38-A See, e.g., 41 Fed. Reg. 5823 (1976); 21 C.F.R. § 81.10 (1978).

38-B E.g., Ferric Ferrocyanide (Iron Blue), 43 Fed. Reg. 54235 (1978).

38-C See Provisionally Listed Color Additives, 42 Fed. Reg. 6992 (1977).

38-D 21 U.S.C. § 376(b), (c), (e). The Color Additive Amendments contain another distinctive feature. This is a provision, 21 U.S.C. § 376(b)(5)(C), (D), that allows the petitioner for a color whose potential carcinogenicity is in issue to request that the matter be referred to a special committee of the National Academy of Sciences. No similar provision is made for resolution of the scientific issues involving other constituents of food with the exception of pesticide residues on raw agricultural commodities. The reference authority for color additives has only been invoked on only ______ occasions.

38-E 21 U.S.C. § 371(e)(2).

38-F See Certified Color Mfgrs. Ass'n v. Mathews, 543 F.2d 284 (D.C. Cir. 1977).

III.D. Indirect Constituents

39-X FDA estimates that there may be as many as 10,000 indirect food additives (including indirect GRAS and prior sanctioned substances. Food Additives Hearings, supra note 32-E, at 57. As of September, 1978, EPA had set tolerances for 268 pesticides for residues on one or more raw agricultural commodities. Of the total of 5,984 individual EPA tolerances, 940 are for chemicals suspected of causing cancer. Cancer Causing Chemicals In Food, Report of the Subcommittee on Oversight and Investigations of the House Committee on Interstate and Foreign Commerce, 95th Cong., 2d Sess. 33 (1978). At least 143 pesticides and animal drugs are known to leave chemical residues in meat and poultry, but only 46 of these substances occurring in edible animal tissue are monitored by the USDA. Id. at 24. In this context "pesticide residues" include only pesticides purposely used on crops for which they are approved, and not residues that may find their way into the food supply through drift to other crops or persistence in the environment.

39-Y Food Additives Hearings at 57. (Statement of Sherwin Gardner, Acting Commissioner of Food Drugs).

40-A 21 U.S.C. § 321(5) (emphasis added).

40-B For example, although acrylonitrile polymers in beverage containers are classified as food additives, some wrapping materials for meat products made from acrylonitrile copolymers have a prior sanction and thus are not classified as food additives. 21 C.F.R. § 181.32 (1978). Some other packaging materials, such as sorbose and acacia, are generally recognized as safe and thus are not subject to regulation as food additive. See 21 C.F.R.

Part 186 (1978).

41-A In 1958 50 parts per million was the smallest amount of material detectable. Today analytical chemistry is able to detect parts per trillion. See Lyons, Up-to-Date Technology, Out-of-Date Regulations, New York Times, December 31, 1978, at ____.

41-B Whilte the statutory definition of "food additive" does not on its face require evidence of actual migration, it might be difficult for FDA to explain why a substance that had been detected in food, even though at very low levels, was not potentially a food additive. FDA is reportedly exploring ways of limiting its obligation to search for minute migrants by establishing criteria for detection methods similar to those it promulgated for animal drugs. See notes 48C-50E infra and accompanying text.

41-C Acrylonitrile Copolymers Used to Fabricate Beverage Containers: Final Decision, 42 Fed. Reg. 48528 (1977).

41-D Acrylonitrile copolymers had received informal FDA approval for use in some food contact applications as early as 1948. Acrylonitrile Copolymers Intended for Use in Contact with Food, 41 Fed. Reg. 23940, 23941 (1976). Certain uses were recognized by FDA as GRAS in ________.

In 1976, the agency amended the existing interim food additive regulation, 21 C.F.R. § 121.2010 (recodified at § 180.22 (1978), to allow use of acrylonitrile copolymers to fabricate containers for non-alcoholic beverages. 41 Fed. Reg. 23940 (1976). The history of FDA's handling of acrylonitrile is set forth in the agency's 1976 amendment and in the Commissioner's decision, supra note 41-C.

41-E 42 Fed. Reg. 48528 (1977).

41-F The evidence relied on by the Commissioner consisted of tests conducted on older containers that contained higher concentrations of acrylonitrile monomer, which was shown to migrate at low levels into beverages and food-simulating solvents. The Commissioner stated that, although the concentration of acrylonitrile monomer in the newer bottles had been reduced, the observation of migration in the older containers made it reasonable to expect that there will be some migration from the newer containers as well. Id. at 48530.

41-G Id. at 48530-31. Some readers of the Commissioner's decision initially expressed skepticism that such a showing could ever be made. Reportedly, however, manufacturers of polyvinyl chloride, another plastic packaging material of considerable commercial importance and a frank carcinogen in man as well as laboratory animals, have preliminarily persuaded FDA's Bureau of Foods that they have devised a method of manufacture that prevents migration of residual vinyl chloride monomer. The method involves reduction of the residual monomer to the lowest achievable levels during synthesis, and vacuum stripping of the material to eliminate all remaining monomer to a level below the capability of chemical analysis. In addition, the manufacturers have proferred plausible support for a theory that, at very low levels, the residual monomer is bound within the plastic and unable to migrate. See 20 Food Chemical News 7 (1978).

42-A See Occupational Exposure to Acrylonitrile, 43 Fed. Reg. 45762 (1978); Standard for Exposure to Vinyl Chloride, 39 Fed. Reg. 35890 (1974).

42-B *See* Identification, Classification, and Regulation of Toxic Substances Posing a Potential Carcinogenic Risk, 42 Fed. Reg. 54157 (1977).

42-C *See* Health Risk and Economic Impact Assessments of Suspected Carcinogens: Interim Guidelines and Procedures, 41 Fed. Reg. 21402 (1976); Pesticide Programs: Registration, Reregistration, and Classification Procedures, 40 Fed. Reg. 28242 (1975). *See also* Toxic Substances Control Act, 15 U.S.C. § 2601 (Supp. 1977).

42-E The legislative history of the Food Additives Amendment does not reveal whether Congress fully appreciated the potential interaction between the expansive definition of "food additive" and the Delaney Clause. The House Report discusses both "intentional" and "incidental" additives together and lists examples considered illustrative of both categories. These include "substances intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food." H. Rep. No. 2284, 85th Cong., 2nd Sess. 3 (1958). Congressman Delaney explained that one event which had prompted him to introduce his amendment was the use of a pesticide chemical known to induce cancer, 104 Cong. Rec. 17420 (1958), but failed to note that pesticide residues fall outside the coverage of § 409 and, thus, beyond the reach of the clause that bears his name. While some members questioned the wisdom of Delaney's proposed definition, none cited cases in which its application would be unsound. *Id*. at 17421-22.

The Senate Report indicates that incidental food additives were to be subject to the Delaney Clause, just as direct additives, and went on to observe:

> . . . [W]e want the record to show that in our opinion the bill is aimed at preventing the addition to the food our people eat of any substances the ingestion of which reasonable people would expect to produce not just cancer but any disease or disability. In short, we believe the bill reads and means the same with or without the inclusion of the [Delaney Clause]. This is also the view of the Food and Drug Administration.

S. Rep. No. 2422, 85th, 2d Sess. 11 (1958).

Although not technically a part of the formal legislative history of the Food Additives Amendment, the original report of the Delaney Committee provides examples of the type of compounds the proponents of the clause hoped to reach. The report alluded to the problem of indirect chemical additives, citing the example of antibiotics used in treating dairy cattle that subsequently appear in milk products. The report also stated that the problem went beyond pesticides and chemical additives, and include paper, fiber and plastics used as food containers, wrappers, and handling equipment. H.R. Rep. No. 2356, 82d Cong., 2d Sess. 4 (1952).

42-F For a revealing discussion of FDA's current position on polyvinyl chloride water pipes, see Vinyl Chloride Polymers In Contact with Food, 40 Fed. Reg. 40529, 40534 (1975). See also Doniger, Federal Regulation of Vinyl Chloride; A Short Course in the Law and Policy of Toxic Substances Control, 7 Ecology L.Q. 497 (1978).

43-A FDA has banned the use of acryonitrile bottles, which yield a concentration of acrylonitrile in the bottled beverage of less than 10 parts per billion (ppb). 42 Fed. Reg. 45828, 45829 (1977). In contrast, saccharin, a direct food additive, is used in concentrations of approximately 400 parts per million (12 milligrams per fluid ounce. See 21 C.F.R. § 180.27 (1978).

FDA is currently considering ways of escaping from this dilemma. One possibility under discussion would be to establish a level of migration below which § 409 would not apply, a level so low that the risk posed by any migrating material could be ignored. As the next section explains, FDA has devised a similar approach for dealing with residues of carcinogenic animals drugs. The distinctive feature of that approach is that the residue level which the agency would ignore, i.e., allow to go uncontrolled, is keyed to the carcinogenic potency of the compound. This feature can more readily be reconciled with the text of the statute governing animal drugs. See notes 48-C et seq. and accompanying text. It remains to be seen whether under the present statute FDA could justify a similar approach to indirect food additives, which are regulated under a provision of the Act that appears to speak in terms of the occurrence, or likely occurrence, of physical migration. See § 201(s) of the Act, 21 U.S.C. § 321(s).

44-A 21 U.S.C. § 321(f). The definition of food additive in § 201(s) does not differentiate between food for humans and food for animals. See 21 U.S.C. § 321(s).

44-B See notes 29-A-29-X supra and accompanying text.

44-C See text accompanying note 33-A supra.

44-D Animal Drug Amendments of 1968 § 101(b), Pub. L. No. 90-399, 82 Stat. 343 (1968).

44-E See 21 U.S.C. § 355.

44-X A "new animal drug" is one that is not generally recognized as safe and effective for its intended uses. 21 U.S.C. 6 321 (w). See 21 U.S.C. § 321(p) (parallel definition of "new drug" for humans). Congress thus excluded from the requirement for premarket approval drugs--human as well as animal--that already enjoyed a reputation among scientific experts as safe and effective. As a practical matter, however, virtually all new chemical entities introduced since 1962 have been subjected to the premarket approxal process.

45-A This result followed from the Act's definition of food additive, which includes any substance whose intended use "results or may reasonably be expected to result in, directly or indirectly, in its becoming a component . . . of any food. . . ." 21 U.S.C. § 321(s).

45-B See S. Rep. No. 1308, 90th Cong., 2d Sess. 1 (1968).

45-X This interpretation, which could hardly be said to fly in the face of the statutory language, also aggravated other competitive inequities. Some producers of additives to animal feed had obtained informal FDA approval for their products in the mid-1950's. These approvals, in the agency's view, constituted "prior sanctions" within the meaning of § 201(s). Thus some manufacturers were able to market feed supplements for growth promotion while others were stifled by FDA's interpretation of the new law. Presentation of Richard Kingham, Esquire, at a course on Food and Drug Law taught to FDA scientists at the University of Virginia School of Law, August 18, 1978.

45-C Drug Amendments of 1962 § 104(f)(1), Pub. L. No. 87-781, 82 Stat. 343 (1962). The principal legislative history of the DES proviso is contained in S. Rep. No. 1744, 87th Cong., 2d Sess.

(1962); H.R. Rep. 2464, 87th Cong., 2d Sess. 5 (1962); H.R. Rep. No. 2426, 87th Cong., 2d Sess. 20 (1962) (Conference Report).

46-A 21 U.S.C. § 348(c)(3)(A). Essentially identical language was incorporated in the Color Additives Amendment, 21 U.S.C. § 376(b)(5)(B), and was later included in the provisions governing approval of new animal drugs that Congress enacted in 1968. 21 U.S.C. § 360b(d)(1)(H).

46-B See 21 U.S.C. §§ 348, 360b; Food Producing Animals; Criteria and Procedures for Evaluating Assays for Carcinogenic Residues, 42 Fed. Reg. 10412 (1977).

46-C Perez, Human Safety Data Collection and Evaluation for the Approval of New Animal Drugs, 3 Journal of Toxicology and Environmental Health 837 (1977).

47-A There is a notable distinction between the statutory procedures applicable to new animal drugs and those applicable to animal feed additives. Under § 512, FDA may not withdraw the approval for a drug without first according the manufacturer an opportunity for an evidentiary hearing unless the Secretary of HEW personally determines that the drug poses an "imminent hazard" to the health of humans. See 21 U.S.C. § 360b(e). Until very recently, FDA had construed "imminent hazard" to include only situations in which the risk of injury is both serious and immediate. Thus the cancer hazard associated with smoking cigarettes would not constitute an "imminent hazard" because of the lengthy latency of the illness, coupled with its close association with prolonged exposure. This narrow definition has been severely criticized by the Subcommittee on Oversight and Investigations of the House Commerce Committee. The Subcommittee contended that "imminent hazard" referred to the potential seriousness of injury and had little to do with the length of time necessary for its occurrence or its likelihood. Regulatory Reform, Subcommittee Oversight and Investigations of the House Committee on Interstate and Foreign Commerce, H.R. Rep. No. ____, 94th Cong., 2d Sess. 292-95 (1976).

The same imminent hazard standard also applies to human drug. The new Secretary of FDA has only invoked this standard once. See Phenformin: Public Hearing, 42 Fed. Reg. 21845 (1977). This ruling, involving a drug in wide use for the treatment of diabetes, may well liberalize FDA's historical interpretaiton of the "imminent hazard" language. Without the involvement of the Secretary, FDA could make withdrawal of a feed additive regulation effective pending a hearing simply by refusing to stay its action even if objections requiring a formal evidentiary hearing were submitted. See 21 U.S.C. § 348(e).

47-B See 21 U.S.C. § 360b(d).

47-C The decision in Hess and Clark, Inc. v. FDA, 495 F.2d 975 (D.C. Cir. 1974), erroneously suggests a contrary conclusion. However, the court's dictum fails to distinguish between the criteria applicable to human drugs and those applicable to animal drugs, which in effect incorporate the "no benefit" formula of the Food Additives Amendment. See Freedman, Reasonable Certainty of No Harm: Reviving the Safety Standard for Food Additives, Color Additives and Animal Drugs, 7 Ecology L.Q. 245 (1978). Moreover, acceptance of the court's implication would have the anomalous result of permitting FDA to consider the benefits of human food "additives" administered to food producing animals in the form of drugs but not the benefits of constituents resulting from the use of additives in the feed of such animals, which remain regulated under § 409.

47-E There are relatively few prior sanctioned additives to animal feed, although FDA did countenance the marketing of DES as an animal feed additive by a few manufacturers prior to 1958. The agency has subsequently sought to limit these approvals and to extinguish them at any opportunity, e.g., when a manufacturer's plant burned down. The few prior sanctioned feed additives are subject to the standards of § 402(a)(1) of the Act. See note 33-X *supra* and accompanying text.

47-F See 21 U.S.C. §§ 360b(a), 321(w).

48-A 21 U.S.C. 321(p)(1),(w)(1). The 1962 Drug Amendments Act contain additional transitional provisions, *see* Pub. L. No. 87-781, § 107, 76 Stat. 781 (1962).

47-D FDA probably could assert authority over the labeling of retail packages of meat and poultry products, although the agency has historically deferred to USDA's regulation in this area. The practical difficulties posed by the jurisdictional overlap aside, the FD&C Act has provided the basis for comparable labeling requirements for other products. For example, the FDA has required manufacturers of hair dyes containing coal for dyes to include a warning that the product contains an ingredient that can penetrate the skin and which causes cancer in laboratory animals. Coal Tar Hair Dyes Containing 4-Methecy-M-phenylendediamine or 4-Methoxy-M-Phenylenediamine sulfate, 43 Fed. Reg. 1101 (1978). The authority of the FDA to require warnings about ingredients has been upheld by the District Court for the District of Columbia. CTFA v. Schmidt, 409 F. Supp. 57 (D.D.C. 1976). Although in that case the agency relied on the "false or misleading" provision applicable to cosmetics, an identical provision is applicable to food. Compare 21 U.S.C. § 362(a) with 21 U.S.C. § 343(a)(1). For a discussion of the overlap between FDA and USDA jurisdiction over labeling of meat and poultry products, see study on Federal Regulation, Volume V: Regulatory Organization Senate Committee on Governmental Affairs, 95th Cong., 1st Sess. 113 (1977).

48-B In 1972 Dr. Klemens Johnson, former Director of the FDA Bureau of Veterinary Medicine's Division of Veterinary Medical Review, prepared a thirty-six page memorandum criticizing the agency's methods for detecting drug residues in food animals. Dr. Johnson also assembled a list of 19 animal drugs which were potentially carcinogenic but for which no adequate method existed for detecting residues. This "Johnson Memorandum" was later the focus of a Congressional investigation resulting from the Bureau Director's attempts to recall all copies of the memorandum and to cover up the report. For a full discussion of the memorandum and subsequent investigations, see HEW Review Panel on New Drug Regulation, Report of the Special Counsel's Investigation of Allegations Relating to the Bureau of Veterinary Medicine Food and Drug Administration (May 1977).

48-C Food Producing Animals: Criteria and Procedures for Evaluating Assays for Carcinogenic Residues, 42 Fed. Reg. 10412, 10413 (1977) (hereafter assays for carcinogenic residues).

48-D Id.

48-E See, e.g., Regulatory Reform, Report of the Subcommittee on Oversight and Investigations of the House Committee on Interstate and Foreign Commerce, H.R. Rep. No. , 94th Cong., 2d Sess. 288 (1976) (nitrofurans); Diethylstilbestrol: Notice of Opportunity for Hearing on Proposal to Withdraw Approval of New Animal Drug

Applications, 41 Fed. Reg. 1804 (1976) (DES); Joint Hearings before the Subcommittee on Health of the Senate Committee on Labor and Public Welfare and the Subcommittee on Administrative Practice and Procedure of the Senate Committee on the Judiciary, 94th Cong., 1st Sess. 243 (1975) (Johnson Memorandum).

48-F *See* Diethylstilbestrol: Notice of Opportunity for Hearing on Proposal to Withdraw Approval of New Animal Drug Applications, 41 Fed. Reg. 1804 (1976). An initial decision by the FDA Administrative Law Judge has upheld withdrawal of approval of the use of DES. See Docket No. 76N, 0002 (Sept. 21, 1978).

49-A [Cite speech by FDA Commissioner or Sherman Gardner --to be completed.]

49-B See notes 42-E - 43-A *supra* and accompanying text.

49-C 42 Fed. Reg. 10412 (1977).

49-D While on its face the regulation merely prescribes the standard to be used in detecting residues, its effect is to establish the criteria for establishing a tolerance. If any residue is not detectable by the FDA approved test, the residue is not legally present even if it might be detected by a more sensitive analytical technique.

49-E Assays for carcinogenic Residues at 10431.

49-F *Id.* at 10421. The only statutory basis for FDA's designation of an "acceptable risk" of 1 in 1,000,000 is the obligation imposed by the DES proviso to develop *some* criteria for approving assay methods. FDA stated that such a risk level could be considered of insignificant public health concern because the risk level was the "maximum, and therefore unlikely, human risk level." *Id.* The specified level of risk is the risk for an individual who consumes the maximum residue levels everyday over a lifetime and is based on the assumption that one-third of the total human diet is composed of meat products. From these conservative assumptions, FDA believes the most likely human risk is several orders of magnitude less than the theoretical "acceptable risk."

50-A Id. at 10436.

50-B In some cases, the prescribed test sensitivity will be only indirectly related to the acceptable level of residue. Because many animal drug residues are metabolic by-products of the ingested drug, the presence of any residue is often calculated from measurements of these by-produces.

50-C Id. at 10436. It should be noted that the regulation specified that application of the approved assay method must reveal no detectable residues when drug is used as intended. Otherwise, the drug cannot be approved.

50-D Id. at 10412. As the preamble to FDA's regulation conceded, the legislative history of the DES proviso provides no clear answer to Congress' intent. One interpretation of the DES proviso is that it was intended to implement the Delaney Clause whenever an animal drug residue, no matter how minute, might occur and that the proviso merely permitted the use of drugs where it had been conclusively shown that the drug left no residues. FDA rejected this interpretation on the ground that it would render the clause a "Catch-22" because modern methods of chemical analysis have confirmed that any drug, no matter how used, will leave some residues albeit perhaps below the level of detection.

50-E Id. at 10419. This decision is itself controversial:

one of the objectives of the regulation was to provide some stability in the regulation of animal drugs, and to forestall continuous pressure to develop even more sensitive methods for detecting residues. The agency's decision does not avoid the uncertainty posed by the possible development of new assays capable of detecting residues below the "acceptable risk" level. It does, however, obviate any obligation on the sponsor or a drug to continue efforts to develop such methods once his product has met the criteria of the regulation.

50-F FDA's February 1977 regulation was invalidated by the United States District Court for the District of Columbia on the ground that the agency had failed to afford manufacturers an adequate opportunity to comment on the scientific bases of its final criteria. Animal Health Institute v. Califano, ____ F. Supp. ____ (D.D.C. 1978). The court's opinion, however, does not suggest that the agency's basic approach is suspect. FDA has revised the regulation and intends to repropose it for further comment. While the revised version may include some significant changes, the agency is likely to adhere to the basic approach described above unless and until the Act is amended.

51-A Residues may also contaminate commodities other than those on which pesticides are used, through drift following initial application or persistence in the environment. When this occurs, FDA currently regulates the residues as environmental contaminants under §§ 402(a) and 406. Thus a single pesticide may be subject to regulation under both § 406 and under § 408 of the Act. But see United States v. Ewig Bros., Inc., 502 F.2d 715 (7th Cir. 1974). The discussion here is concerned exclusively with Federal efforts to regulate residues on raw agricultural commodities for which a pesticide has been specifically approved and in processed foods derived fom those commodities.

51-B Responsibility for this function formerly rested with FDA, and authority to register pesticides with the Department of Agriculture. See generally Renkanf, Regulation of Agricultural Pesticides, 62 Iowa L. Rev. 909 (1977). The reassignment in 1970 of responsibility for establishing tolerances under § 408 did not alter FDA's role as the agency responsible for monitoring compliance within EPA tolerances. Reorg. Plan No. 3 of 1970, 3 C.F.R. 1072 (1970), reprinted in 5 U.S.C. App. II, at 60 (1978).

51-C 7 U.S.C. §§ 121-136y. In 1972, Congress substantially revamped the existing statutory scheme for pesticide control when it passed the Federal Environmental Pesticide Control Act, Pub. L. No. 92-516. The law provided a period for transition to permit reregistration, in accordance with new, more demanding standards of safety, of all pesticides previously registered under FIFRA. In 1978, Congress again amended the statutory scheme for pesticide control to permit the conditional registration of pesticides during the period in whichthe data needed for complete registration was being generated. The amendments also sought to expedite the registration process by permitting the EPA to register pesticides on a generic basis. See Federal Pesticide Act of 1978, Pub. L. No. 95-396.

51-D 21 U.S.C. §§ 342(a)(2)(B), 346a(a).

51-E 7 U.S.C. § 136a(a).

51-F 7 U.S.C. § 136a(C)(5).

52-A 7. U.S.C. § 136(bb).

52-B Health Risk and Economic Impact Assessments of Suspected Carcinogens, 41 Fed. Reg. 21402 (1976).

52-C Id. See also EPA Regulations for Enforcement of FIFRA, 40 C.F.R. § 162.11 (1976).

52-X EPA has established a set of rebuttable presumptions against registration to aid in determining whether a pesticide is likely to cause unreasonable adverse effects. A rebuttable presumption arises if the pesticide exceeds specified cirteria for any of three types of effects: (1) acute toxicity; (2) chronic toxicity; or (3) lack of emergency treatments for exposed humans. Acute toxicity is defined in terms of minimum lethal dosages for both animals and wildlife. Chronic toxicity is defined in terms of oncogenic or mutagenic effects. Lack of emergency treatments is defined as whether there is a known antidotal, pallative, or first aid treatment for amelioration of toxic effects in man resulting from a single exposure.

The effect of these rebuttable presumptions is to shift to the applicant or registrant the burden of demonstrating: (1) for a pesticide indicating found to be acutely toxic and that, when considered with proposed restrictions on use and widespread and commonly recognized practices of use, the pesticide is not likely to result in any significant acute adverse effects; or (2), for a pesticide initially found to be chronically toxic that, when considered with proposed restrictions on use and common practices of use, the pesticide will not concentrate, persist, or accrue to levels likely to result in any significant chronic adverse effects; or (3), for any pesticide, that EPA's determination that it exceeds the criteria for risk was in error. Alternatively or in addition the applicant may submit evidence to demonstrate that the economic, social, and environmental benefits of the use of the pesticide outweigh the risk of use. See 40 C.F.R. § 162.8 (1976).

While the EPA gives special consideration to the carcinogenic potential of a pesticide, see Health Risk and Economic Impact Assessments of Suspected Carcinogens, 41 Fed. Reg. 21402 (1976), the agency may still permit registration if the pesticide's economic benefits outweigh the health risk. See Regulatory Reform, Hearings Before the Subcommittee on Oversight and Investigations of the House Committee on Interstate and Foreign Commerce, 94th Cong., 2d. Sess. 198 (1976).

52-D See 21 U.S.C. § 321(s).

52-E 21 U.S.C. § 321(s)(1).

52-F 21 U.S.C. § 342(a)(2)(B(.

52-G Act of July 22, 1954, Pub. L. No. 83-518, § 2, 68 Stat. 511 (1954).

53-A 21 U.S.C. § 346a(a).

53-B Few pesticides qualify for this exception. See Food Additives Hearings at _____.

53-C 21 U.S.C. § 346a(b).

53-D See note 52-E supra and accompanying text.

54-A So far as the author is aware, this has occurred only rarely. One recent example occurred in the summer of 1977, when EPA authorized the use of a carcinogenic pesticide, BAM, on two critical crops in Oregon and Idaho. 42 Fed. Reg. 37437 (1977). A similar exemption was granted in February 1978 for certain crops in California and Utah. 43 Fed. Reg. 5884 (1974). In both cases the EPA determined that economic consequences of failing to permit the use of the pesticide outweighed the minimal health hazard resulting from its limited use and occurrence as residues in foods. [Another example to be provided.]

54-B _See_ Cancer-Causing Chemicals--Part 2: Chemical Contamination of Food, Hearings before the subcommittee on Oversight and Investigation; House Committee on Interstate and Foreign Commerce, 95th Cong., 2d Sess. ____ (1978).

54-C See note 52-E _supra_ and accompanying text.

54-D See notes 26-B - 29-X _supra_ and accompanying text.

54-E 21 U.S.C. § 342(a)(2)(C).

54-F The legislative history of the 1958 Food Additive Amendments does not explain why Congress chose to exempt pesticide residues on processed foods. Presumably it concluded that the evaluation of safety performed under § 408 was adequate to protect consumers so long as the amount of residue did not exceed that authorized for the raw commodity. But there is no evidence it was sensitive to the fact that the applicable criteria for evaluation under §§ 408 and 409 are not the same.

55-A 21 U.S.C. § 342(a)(2)(C).

55-B Cancer-Causing Chemicals--Part 2: Chemical Contamination of Food: Hearings Before the Subcommittee on Oversight and Investigations of the House Committee on Interstate and Foreign Commerce, 95th Cong., 2d Sess. 30 (1978).

55-C _See_ 21 U.S.C. § 342(a_(2)(C).

56-A _See_ notes 26-A - 28-A _supra_ and accompanying text.

56-B _See_ 21 C.F.R. Part 193.

56-C In administering § 409 of the FD&C Act, EPA is presumably bound by the Delaney Clause as FDA would be.

56-D EPA would of course have to determine that this higher level would meet the more general safety criteria of § 408 of the Act. See 21 U.S.C. § 346a.

57-A 21 U.S.C. § 346a(d)(1)-(2). [Is this ever denied? Answer to be obtained.]

57-B 21 U.S.C. § 346a(d)(3), (5).

57-C 21 U.S.C. § 346a(d)(5).

57-D See notes 29-A - 29-X supra and accompanying text.

APPENDIX C

A COMPARISON OF FDA FOOD SAFETY REGULATION WITH FEDERAL REGULATION OF OTHER ENVIRONMENTAL HAZARDS

Prepared for the Committee

By

Jeffrey Trauberman

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The tables in this appendix compare the regulation of carcinogens and other toxic substances by various federal agencies acting under authority conferred by different statutes. These tables are presented in partial fulfillment of the statutory charge to the National Academy of Sciences under the Saccharin Study and Labeling Act to study

> ...the relationship between existing Federal food regulatory policy and existing Federal regulatory policy applicable to carcinogenic and other toxic substances used as other than foods.

A Description of the Tables

The first column heading, reading from left to right, includes the name of the statute, the date of enactment and any major or recent amendments, the agency administering the act, and a brief description of the jurisdictional scope of the statute.

The second column lists the statutory standard for regulatory action and is subdivided into a sub-column headed "Standard," which describes or paraphrases particular statutory language, and a sub-column labeled "Regulatory Decision or Action," which lists the type of regulatory decision governed by that statutory language.

The next column, headed "Agency Concerns in Regulatory Action" is subdivided into "Benefits?" and "Risks." The benefits sub-column describes whether and how the agency considers economic or technologic benefits in regulating hazards. It is concerned not only with agency actions as a result of statutory authorization, but also with agency practices arising out of judicial interpretation or agency discretion. The sub-column on risks does not show whether risks are evaluated—in all cases they are--

but focuses, instead, on the type of risks considered by the agency, and the sort of evidence used by the agency in determining those risks.

The next column states whether the agency commonly employs risk-benefit analysis in its decision-making—that is, whether a systematic quantification and balancing of risks and benefits of regulatory action is undertaken by the agency.

The column on "Agency Emphasis on Mutagens, Carcinogens, or Teratogens" describes the extent to which the agency is required, or has in fact, singled out for special regulatory consideration those substances suspected of having carcinogenic, mutagenic, or teratogenic effects. It is followed by a column describing the amount of statutory discretion which the agency has in regulating these hazards, that is, whether the agency is required to take certain action with respect to such substances.

The next column summarizes the rulemaking procedures used by the agency. Such procedures include informal notice and comment rulemaking, formal adjudicatory rulemaking and hybrids of these two approaches.

The next to last column on "Systematic Approaches to Information Gathering" describes the ways in which the agencies acquire information. Examples are manufacturers' recordkeeping or testing requirements, advisory committees, inspections, and research programs.

The last column lists selected remedies available to the agency, including the penalties for violating the statute, unusual regulatory programs undertaken by the agency, and any other relevant information.

Limitations of the Tables

Some limitations of this tabular method of comparing environmental regulation among agencies should be noted. The tables do not depict federal regulatory policies comprehensively. The depicted statutes and statutory provisions have been chosen selectively to provide a representative overview of current federal regulatory policies. Second, the tables are not designed to guide lawyers or other experts through the intricacies of the individual statutes. An attempt to delineate entire, frequently complex safety laws would be beyond the scope of this study. Finally, in preparing the tables, it often was necessary to paraphrase and draw conclusions from statutory language, agency statements, judicial opinions, and other expert commentaries. However, all the tables were reviewed by officials of the appropriate agencies to assure a more accurate reflection of current regulation.

Selected Conclusions Involving Food Safety Regulation

The tables demonstrate that the food provisions of the Federal Food, Drug, and Cosmetic Act are relatively complex—perhaps more so than those of any other regulatory statute. The complexity may result in part from the comparatively lengthy history of federal regulation of foods which, in turn, has allowed extensive refinements to be made in the contours of regulation. While this historical refinement may create a sense of greater regulatory predictability, the regulation of the vast stream of commerce in food products and food additives also has led to a pervasive federal presence of extraordinary breadth and complexity.

The complexity of the law is partly a function of the statutory classification system. This system, which is not easily understood, establishes many categories of food substances, each of which is regulated under a different standard. In addition, these standards are not necessarily commensurate with risk, but rather, may be based on historical use and the route of entry into the food supply. A substance defined as a food additive must be proved safe and may not cause cancer in humans or animals, or else it is subject to a ban. However, if the same substance is a natural constituent of food (which means that it is not considered "added"), the food may be banned only if the substance renders the food "ordinarily... injurious to health."

The tables suggest that other regulatory statutes are more consistent than the food safety provisions of the Federal Food, Drug, and Cosmetic Act in linking perceived risks and benefits to regulatory decisions and classifications. For example, that Act is virtually the only regulatory statute reviewed here that precludes consideration of benefits in regulating carcinogens and attempts to eliminate agency discretion in this aspect of the regulatory process. Even the Toxic Substances Control Act, which requires the Environmental Protection Agency to initiate "appropriate action" when it obtains evidence that a chemical is carcinogenic, leaves the regulatory consequences primarily within the discretion of the agency.

Other statutes speak in such terms as "unreasonable risk," "unreasonable adverse effects," or protection from hazards to the extent "feasible." These criteria permit or even require the regulator to consider economic and other benefits. Still other statutes are even more explicit, and include language requiring the agency to consider the economic, environmental, and technologic consequences of regulating a particular hazard. For example, the Toxic Substances Control Act mandates that EPA should give detailed consideration in regulating a chemical to the health and environmental risks of the chemical, the availability of substitutes, and the economic and technologic consequences of the regulatory action. Similarly, the Federal

Insecticide, Fungicide, and Rodenticide Act requires EPA to consider in its regulatory decisions the "economic, social, and environmental costs and benefits" of using a pesticide. Interestingly enough, though this act requires EPA to give great weight to benefits, the agency has implemented the statute to establish a rebuttable presumption against approving carcinogenic pesticides, thus severely inhibiting the registration of such products.

A related distinction between the food provisions of the Federal Food, Drug, and Cosmetic Act and other federal regulatory statutes is the extent to which the standards for food regulation imply that an absolute measure of food safety exists. Food additives are considered either safe or unsafe, and there is scant statutory provision for the use of intermediate regulatory consequences or approaches, such as labeling. Other environmental laws provide several statutory classifications and regulatory alternatives for hazards of varying risks and benefits, and establish a goal expressed in terms of reasonableness rather than safety.

The tables also show that FDA is not alone in eschewing the use of risk-benefit analysis. The lack of a technical, political, and moral consensus on the value of risk-benefit analysis is reflected throughout the federal government. Risk-benefit analysis, in the sense of a formal and explicit balancing process, is used only to regulate noise sources under the Noise Control Act and drugs under the Federal Food, Drug, and Cosmetic Act. However, courts on occasion have struck down agency actions that were based on an assessment of risks without significant consideration of health and non-health benefits.

A comparison of the rulemaking procedures under the various statutes reveals several differences between food safety regulation and the regulation of other environmental hazards. While many agencies may employ advisory committees and technical panels in the rulemaking process, FDA is one of the few that in selected circumstances is required to empanel an advisory committee before taking regulatory action. Also, FDA seems to rely more than most agencies on "formal" rulemaking, which involves cumbersome, trial-type proceedings. The more expiditious process of notice-and-comment rulemaking is not employed in certain important regulatory decisions on food safety, most notably in food additive regulation, tolerance-setting, and color additive listing and certification. Strangely enough, FDA's formal rulemaking procedures (specified in Section 701(e)-(g) of the Act) must also be used by the Consumer Product Safety Commission in regulating certain hazardous substances under the Federal Hazardous Substances Act.

Further inspection of the tables reveals other regulatory patterns and developments. Some agencies propose to regulate carcinogens "generically". For example, both the Occupational Safety and Health Administration and the Consumer Product Safety Commission have indicated an intent to regulate potential carcinogens by grouping them in separate categories based on the type of scientific evidence available. Within each category, substances would be subject to similar overall regulatory requirements. Such a proposal is designed to expedite the regulatory process by eliminating the need for "substance-by-substance" relitigation of the fundamental scientific and legal issues which arise in regulating potential carcinogens.

Another observation that can be derived from the tables is that there are many agency approaches to gathering data and establishing regulatory priorities. Most agencies, including FDA, employ advisory committees, require industry to record or submit certain safety information, and fund or conduct research activities. Other agencies, with varying degrees of success, rely on more systematic methods. The Consumer Product Safety Commission, for example, uses a computer network to monitor selected hospital emergency rooms and to rank certain consumer products according to risk. Still another systematic approach to setting regulatory priorities is represented by the activities of the Interagency Testing Committee in recommending a discrete number of chemicals for testing under the Toxic Substances Control Act.

Regulatory enforcement mechanisms and remedies also vary among agencies. Nearly all agencies may institute civil and/or criminal proceedings to enforce statutory or regulatory requirements. Seizure of offending products or substances is a particularly common remedy. Other enforcement devices include the authority to order the recall, repair, or replacement of non-complying products or substances. More recently, provisions for citizens' suits have been included in several regulatory statutes, notably the Noise Control Act, the Toxic Substances Control Act, and the Safe Drinking Water Act, allowing private individuals to sue the government to enforce particular statutory or regulatory requirements. Other regulatory trends apparent from the tables are increased reliance on the voluntary efforts of industry to achieve goals of environmental regulation, and a tendency to allow greater state assumption of regulatory responsibilities.

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The following tables are based on:

- The food provisions of the Federal Food, Drug, and Cosmetic Act (contained in 21 U.S.C. 348 et seq)
- The drug provisions of the Federal Food, Drug, and Cosmetic Act (contained in 21 U.S.C. 348 et seq)
- The medical devices provisions of the Federal Food, Drug, and Cosmetic Act (contained in 21 U.S.C. 348 et seq)
- The cosmetic provisions of the Federal Food, Drug, and Cosmetic Act (contained in 21 U.S.C. 348 et seq)
- The Federal Meat Inspection Act (21 U.S.C. 601 et seq) and the Poultry Products Inspection Act (21 U.S.C. 451 et seq)
- The Federal Hazardous Substances Act (15 U.S.C. 1261 et seq)
- The Consumer Product Safety Act (15 U.S.C. 2051 et seq)
- The Occupational Safety and Health Act (29 U.S.C. 651 et seq)
- The Noise Control Act (42 U.S.C. 4901 et seq)
- The Toxic Substances Control Act (15 U.S.C. 2601 et seq)
- The Safe Drinking Water Act (42 U.S.C. 300 et seq)
- The Clean Air Act (42 U.S.C. 7401 et seq)
- The Federal Insecticide, Fungicide, and Rodenticide Act (7 U.S.C. 136 et seq)

Statute (date of enactment and major amendment(s)), Agency, and Jurisdiction	STATUTORY STANDARD FOR REGULATORY ACTION: Standard	STATUTORY STANDARD FOR REGULATORY ACTION: Regulatory Decision or Action	AGENCY CONCERNS IN REGULATORY ACTION: Benefits?
FOOD, DRUG, AND COSMETIC ACT (original statute enacted in 1906; major overhaul in 1938; major amendments in 1958, 1960 and 1968) o Administered by the Food and Drug Administration (FDA) o Regulates foods, drugs, cosmetics, medical devices, and substances therein FOOD PROVISIONS	Food Provisions:		
	A. Raw agricultural commodities and their natural constituents (ex: vitamin C in orange juice): Food containing any poisonous or deleterious substances which "ordinarily" renders it injurious to health	A. Deeming a food to be adulterated if the poisonous or deleterious substance isn't "added".	A. Yes - Though the act neither authorizes nor precludes benefit consideration
	B. Contaminants (ex: aflatoxin in peanuts):		
	1. Substances considered "added" to food which are required or unavoidable by good manufacturing practice and which "may render" food injurious to health	1. Establishment of a tolerance level for an "added" poisonous or deleterious substance, or an "action level" for regulatory intervention. If this tolerance or action level is exceeded, the food is deemed adulterated	1. Yes - Considering unavoidability by good manufacturing practices involves economic and technologic feasibility
	2. Substances considered "added" to food which are avoidable by good manufacturing practice and "may render" the food injurious to health	2. Deeming a food to be adulterated for containing such a substance	2. No
	C. Direct Ingredients:		
	1. Direct Food Additive (ex: saccharin):	1. FDA approval of a direct food additive	
	a. "safe" for its intended use, functionally capable of accomplishing its intended effects, and		a. Yes - Functionality
	b. Does not induce cancer in man, or through "appropriate" tests, in animals (Delaney Clause)		b. No
	2. Substances Generally Recognized as Safe (GRAS; ex: salt): Among qualified experts, substances generally recognized as safe for their intended uses	2. Exemption from the food additives provisions of the act (Delaney Clause does not apply)	2. Yes - Established usages
	3. Prior Sanctioned Substances (ex: nitrites in meat): Substances used historically with the sanction or approval of FDA and USDA before September 6, 1958.	3. Recognition of a prior sanction exemption from the food additives provisions of the act (Delaney Clause does not apply)	3. Yes - Though not explicitly authorized, FDA considers some benefits of use of the substance

AGENCY CONCERNS IN REGULATOR ACTION Risks	Routine, Rigorous Risk-benefit Analysis?	Agency Emphasis on Mutagens, Carcinogens, or Teratogens?	Agency Discretion in Regulating Mutagens, Carcinogens, or Teratogens?	Procedure for Issuing Regulations	Use of Systematic Approaches to Information Gathering, or Testing	Selected Other Regulatory Initiatives, Enforcement Efforts, or Devices
A. FDA employs Minimum Clinical Effect Levels to establish levels at which humans might be injured; courts require FDA to show a reasonable possibility of harm before acting, rather than a mere speculative risk	A. No	A. No	A. Yes	Informal rulemaking with notice and subsequent comment, except in certain circumstances, party adversely affected by agency action may request a hearing. These special circumstances arise in proceedings related to: • food standards • foods for special dietary uses • emergency permit controls • tolerances • food additive regulations • antibiotic animal drug certifications • new animal drug applications • color additive listings and certifications	• Advisory Committees • Agency testing and research • Monitoring of industries • Requests for data from manufacturers • Requirements of data submission by manufacturers seeking premarket approval of additives	• Labeling, nutritional information disclosure • GRAS list review • Inspections of industry • Seizure, condemnation, recall of adulterated or misbranded substances • Criminal penalties • In addition to rulemaking FDA simply may go to court over particular instances of food adulteration or misbranding
B. FDA must consider protection of public health and alternate modes of exposure to the substance	B. No	B. No	B. Yes			
	1. No	1. Yes	1. No			
a. Safety - FDA is required to consider consumption levels, cumulative effects, and expert approved safety factors b. Appropriate tests evidencing carcinogenicity in man or animal are dispositive						
2. GRAS regulations contain standards for evaluating food risks	2. No	2. Yes-It has been suggested that evidence of carcinogenicity would destroy any basis for "general recognition" of safety	2. Yes			
3. Risks or prior sanctioned substances evaluated similarly to those of added constituents - standard for regulatory action is whether substance "may render" food injurious to health	3. No	3. No	3. Yes			

Statute (date of enactment and major amendments); Agency, and Jurisdiction	STATUTORY STANDARD FOR REGULATORY ACTION		AGENCY CONCERNS IN REGULATORY ACTION
	Standard	Regulatory Decision or Action	Benefits?
Food, Drug, and Cosmetic Act: Food Provisions (cont'd)	4. Color Additives (ex: Red No. 40):		
	a.1. Safe for its intended use and accomplishes its intended effect, or	a.1. Obtaining FDA approval of a color additive (including establishment of permitted levels of use)	4a. Functionality is the primary benefit considered
	a.2. Used and approved prior to 1960,	a.2. Obtaining temporary, provisional listing of color additive	
	b. But, if it induces cancer in man, or through "appropriate" tests, in animals	b. Revoking FDA approval of a color additive	4b. No-This "Delaney Clause" applies to all color additives (there is no GRAS or prior sanction exemption)
	D. "Indirect" Ingredients:		
	1. Indirect Food Additives (ex: acrylonitrile packaging materials) which "may reasonably be expected" to become a component of food	1. Regulation of indirect additives is similar to the regulation of intentional food additives (Delaney Clause, GRAS exemptions, prior sanctions apply)	1. See considerations for intentional food additives
	2. Animal Drug Residues (ex: sulfanomide) a. safe and efficacious in animals, b. residues are safe for humans, and c. no residues of any carcinogenic drug can be found in edible portions of animals by "approved" methods.	2. Obtaining FDA approval or sanction of animal drugs	2. Yes-The animal drug "Delaney Clause" is modified by a "DES proviso" that allows carcinogenic animal drugs to be used that don't adversely effect the animal recipients or leave residues detectable by "approved" methods
	3. Pesticide Residues (ex: heptachlor) - EPA has primary responsibility in this area		3. Yes - Delaney Clause doesn't apply to pesticide residues
	a. In raw foods if		a. Must show pesticides "useful" for the purpose for which tolerance is sought, and necessary to the food supply. Also, FDA must consider impact of its action on food prices and food supply to consumers.
	1. poisonous or deleterious pesticides, or pesticides not generally recognized as safe are used.	1. Tolerance level required	
	2. tolerance levels not necessary to protect public health	2. Exemption from tolerance level requirement	
	b. In processed foods if tolerance has been established, processing hasn't concentrated the pesticide, good manufacturing practices are followed	b. Pesticide deemed "safe" as an "additive"	b. In evaluating the extent to which "good manufacturing practice" has been followed in processing, some economic benefits may be considered.

AGENCY CONCERNS IN REGULATOR ACTION Risks	Routine, Rigorous Risk-benefit Analysis?	Agency Emphasis on Mutagens, Carcinogens, or Teratogens?	Agency Discretion in Regulating Mutagens, Carcinogens, or Teratogens?	Procedure for Issuing Regulations	Use of Systematic Approaches to Information Gathering, or Testing	Selected Other Regulatory Initiatives, Enforcement Efforts, or Devices
4a. Safety-FDA is required to consider probable consumption levels, cumulative effects, expert approved safety factors and the availability of certain analytic methods	4. No	4. Yes-Special advisory committees may be established when carcinogenicity is an issue in listing color additives	4. No			
4b. Appropriate tests evidencing carcinogenesis in man or animal are dispostive						
1. FDA says "reasonably be expected to migrate" does not require that analytic methods must actually be able to detect residues in food, but that diffusion of a chemical within a substance creates a presumption of migration. Toxicologic data is examined, along with data from "food simulating" solvents. (Also, see considerations for intentional food additives)	1. No	1. Yes	1. Yes-for GRAS and prior sanctioned substances. No for others			
2. Safety - depends on probable consumption levels, cumulative effects on humans and animals, expert approved safety factors, and expected conformity of usage with labeling requirements Residues - FDA requires manufacturer to show extrapolated cancer risk of less than 1 in a million over a lifetime	2. Limited to determing safety and efficacy in animals. Not for determining safety of residues	2. Yes	2. Yes			
3. "Zero tolerances" are authorized, though carcinogens are not required to be banned	3. No	3. Yes - EPA guidelines on carcinogens exist	3. Yes			

Statute (date of enactment and major amendments), Agency, and Jurisdiction	STATUTORY STANDARD FOR REGULATORY ACTION Standard	 Regulatory Decision or Action	AGENCY CONCERNS IN REGULATORY ACTION Benefits?
DRUG PROVISIONS of the Food, Drug, and Cosmetic Act	A. Drugs which: 1) consist in whole or part of filthy, decomposed or putrid substances 2) are manufactured or processed under substandard conditions 3) will not have their purported affects 4) contain unsafe color additives 5) contain (or are) unsafe animal drugs.	A. Classification of a drug as adulterated	Yes-Evaluation of efficacy by FDA involves considering clinical, pharmacologic, and therapeutic benefits
	B. Drugs which: 1) are labeled in a false or misleading manner 2) are not labeled as required by law 3) are dangerous when used in the manner suggested by the label 4) purport to be insulin or certain antibiotics but are not appropriately batch-certified.	B. Classification of a drug as misbranded	
	C. Drugs (except new animal drugs or animal feed containing a new animal drug) which: 1) are not generally recognized as safe and effective for the use and conditions stated on the label, or 2) have not extensively been used under the proposed conditions, or 3) have not been regulated and labeled similarly under the 1906 Food and Drug Act.	C. Classification of a drug as a new drug, requiring FDA approval of a new drug application (NDA)	
	D. Drugs which: 1) are habit-forming, or 2) require the supervision of a physician to be used safely.	D. Classification of a drug as a prescription, rather than over-the-counter, drug	
	E. New drugs which: 1) are not proven "safe" 2) are not shown by substantial evidence (based on expert investigation) to have their purported effect (efficacy) 3) are improperly labeled, or 4) are improperly processed or packaged	E. Disapproval of a new drug application; withdrawal of approval of new drug application (1-3 only)	
	F. New drugs which pose an imminent hazard to the public health	F. Immediate suspension of approval of new drug application	

AGENCY CONCERNS IN REGULATOR ACTION

Risks	Routine, Rigorous Risk-benefit Analysis?	Agency Emphasis on Mutagens, Carcinogens, or Teratogens?	Agency Discretion in Regulating Mutagens, Carcinogens, or Teratogen	Procedure for Issuing Regulations	Use of Systematic Approaches to Information Gathering, or Testing	Selected Other Regulatory Initiatives, Enfor ment Efforts, or Devices
• Generally, determining "safety" involves evaluating health risks to humans or animals using data from laboratory, animal, and human experiments, as well as that from inadvertent or occupational exposure • Health risks from new drugs more closely evaluated than from drugs with established usages. Incidence and risk of adverse reactions and significant side effects when used according to directions and potential for misuse are evaluated in classifying drugs as prescription or over-the-counter. Also, the seriousness of the disease being treated is important in this classification Evidence obtained from "investigational" use of the new drug is evaluated in approving new drug applications. Evidence obtained subsequent to approval is emphasized in withdrawing approval of a new drug application	• Yes-New drugs are evaluated in risk-benefit terms. The risk of using the new drug is balanced against the benefits of use in setting "socially acceptable" levels of risk • Most drugs with established usage are not systematically subject to risk-benefit analysis; however, when sufficient evidence of adverse health effects from established drugs appears, risk-benefit analysis may be undertaken • Determination of adulteration or misbranding rarely involves risk-benefit analysis.	Evidence of carcinogenic, mutagenic, or teratogenic effects most important in evaluating new drugs rather than existing drugs, and in classifying drugs as either over-the-counter or prescription	Yes	Informal notice and comment rulemaking, except an aggrieved party may request a hearing in decisions involving: • prescription drug advertising • insulin regulations • antibiotic drug certifications • drugs liable to deterioration • strength, quality, and purity of drugs • new drug application requirements • habit-forming drugs	• Advisory committees for new drug applications • In-house review of new drug applications • Testing of existing drugs is not very frequently undertaken • Special consultants • Industry data heavily relied on • New drugs for chronic use are tested for two years in one or two species of rodents to determine potential human health effects.	• General review of existing data on over-the-counter drugs is currently being conducted • In addition to rulemaking FDA simply may go to court over particular instances of drug adulteration or misbranding • See "foods" for other enforcement devices

Statute (date of enactment and major amendments), Agency, and Jurisdiction	STATUTORY STANDARD FOR REGULATORY ACTION		AGENCY CONCERNS IN REGULATORY ACTION
	Standard	Regulatory Decision or Action	Benefits?
MEDICAL DEVICES PROVISIONS (enacted in 1976) of the Food, Drug, and Cosmetic Act	A. See drugs section on adulteration	A. Deeming a device to be adulterated	Yes - Health benefits are evaluated in assessing the safety and efficacy of a medical device under the act.
	B. See drugs section on misbranding	B. Deeming a device to be misbranded	
	C. If "general controls" (includes provisions on adulteration and misbranding, as well as certain other statutory provisions) are: 1. Sufficient to establish the safety and effectiveness of a device, or 2. Insufficient to ensure safety and effectiveness, but: • the device is not used to sustain life or of substantial importance in preventing impairment of health, and • It does not pose an "unreasonable" risk to human health	C. Classifying a device as "Class I", requiring only the application of "general controls"	
	D. If "general controls" are insufficient to provide reasonable assurance that a device is safe and effective	D. Classifying a device as "Class II", requiring it to comply with FDA "performance standards" in addition to "general controls"	
	E. If both general controls and performance standards are insufficient to reasonably assure the safety and effectiveness of a device, and: • The device is used to sustain life or is of substantial importance in preventing impairment of health, or • it presents a potential "unreasonable" risk to human health	E. Classifying a device as "Class III", requiring FDA premarket approval, in addition to "general controls"	
	F. If: 1. There is no reasonable assurance that the device is safe or effective under the conditions stated in the label, or 2. "Good manufacturing practices" are not being followed in the production of the device, or 3. The labeling is false or misleading, or 4. The device does not comply with a performance standard and an insufficient reason exists for deviating from that standard, or 5. The manufacturer has inadequately maintained or provided access to records, or has failed to register as a manufacturer of a device	F. Revocation of premarket approval of a device; Refusal to grant premarket approval of a device (1-4 only).	
	G. If other regulatory methods fail to provide reasonable assurances of safety and effectiveness of a device	G. Authorization to restrict the use, sale, or distribution of a medical device by written or oral "prescription" or otherwise as required by FDA	
	H. If a device presents "substantial deception" or "unreasonable and substantial risk of illness or injury", and labeling has not been undertaken that would sufficiently reduce substantial deception	H. Banning a device (can be done immediately)	

AGENCY CONCERNS IN REGULATORY ACTION

Risks	Benefits, Rigorous Risk-Benefit Analysis?	Agency Emphasis on Mutagens, Carcinogens, or Teratogens?	Agency Discretion in Regulating Mutagens, Carcinogens, or Teratogens?	Procedures for Issuing Regulations	Use of Systematic Approaches to Information Gathering, or Testing	Selected Other Regulatory Initiatives, Enforcement Efforts, or Devices
Agency frequently faced with devices with faulty design, improper functioning, contamination, and improper use - often risk arises after surgical implantation of a device. In vitro tests, tests on laboratory animals, and tests involving human investigational use of the device are evaluated.	Yes-Safety and efficacy are determined by balancing health risks and health benefits under the act.	No	Yes	• Classification of devices marketed before May 1976 as Class I, II, or III - notice and comment rulemaking (petitions for classification are also possible). New or unique devices automatically classified as Class III unless specifically reclassified by FDA. • Performance standards-FDA publishes an invitation to the public (includes contractors and other federal agencies) to develop a proposed standard. Existing federal standards may be proposed or FDA may propose its own standard. In all cases, notice and comment rulemaking follows • Requiring premarket approval of a device marketed before May, 1976-notice and comment rulemaking. No rulemaking required for new, unique Class III devices. • Banning a device-may be effective on publication of proposal in certain cases. Opportunity for an informal hearing required • Good manufacturing practice regulations - oral hearing required • Investigational use exemptions - may be granted without following rulemaking procedures. • Withdrawal of investigational use exemption - informal hearing required	• Advisory committees for classifying devices, and for review of performance standards, good manufacturing practice regulations and orders, premarket approval applications. • Investigations for establishing the effectiveness of a device may be undertaken. • Reports and records must be maintained by manufacturers. • Investigational use exemptions from premarket approval procedure.	• Manufacturer's warnings of device defects • Refund of purchase price, repair, replacement of a defective device • "Good manufacturing practice" rules • Attempts to regulate device "users" (usually health care professionals) being studied • High priority given to regulating cardiac monitoring systems, defibrillators (used to halt irregular beating of the heart), devices used to restore breathing in emergencies, and other life supporting devices. • FDA authorized to exempt devices from strict regulation for investigational purposes (FDA regulation not yet effective) • Labeling (e.g. IUD's, hearing aids) • Voluntary or FDA requested recalls used frequently to remove violative products from the market

	STATUTORY STANDARD FOR REGULATORY ACTION		AGENCY CONCERNS IN REGULATORY ACTION
Statute (date of enactment and major amendments); Agency, and Jurisdiction	Standard	Regulatory Decision or Action	Benefits?
COSMETIC PROVISIONS of the Food, Drug, and Cosmetic Act	A. If a cosmetic: 1) bears or contains any poisonous or deleterious substance which may render it injurious to health under the conditions prescribed in the label, or under such conditions of use as are customary or usual, or 2) consists in whole or in part of any filthy, putrid, or decomposed substance, or 3) has been prepared, packed, or held under insanitary conditions or 4) has a container composed of any poisonous or deleterious substance which may render the contents injurious to health, or 5) contains an unsafe color additive (as defined in the act), except for hair dyes.	Deeming a cosmetic to be adulterated	Very limited - FDA considers most cosmetics to have no significant health benefits
	B. If a cosmetic is labeled in a false or misleading manner	Deeming a cosmetic to be misbranding	
FEDERAL MEAT INSPECTION ACT (enacted in 1906, major amendments in 1967 and 1970); POULTRY PRODUCTS INSPECTION ACT (enacted in 1957, amended most recently in 1968) • Administered by U.S. Department of Agriculture (USDA) • Regulate red meat and red meat food products, poultry and poultry products • Jurisdictional question concerning control of food additives and pesticide residues in meat and poultry addressed by memorandum of understanding between USDA, FDA and EPA, respectively. For food additives FDA determines safety and USDA decides whether it can be used in meat; for pesticides EPA sets tolerances with which USDA usually agrees. In both cases, however, USDA can set stricter standards than FDA or EPA	If any meat or poultry product: • Contains poisonous or deleterious substances • Contains any pesticide, chemical, food additive, or color additive that is unsafe under the Food, Drug, and Cosmetic Act • Has been prepared, packed or held under unsanitary conditions • Is statutorily proscribed or deemed unfit for human consumption	Deeming meat or poultry to be adulterated	Yes - USDA officials indicate that some benefits are evaluated in determining an "acceptable risk"

AGENCY CONCERNS IN REGULATORY ACTION Risks	Routine, Rigorous Risk-Benefit Analysis?	Agency Emphasis on Mutagens, Carcinogens, or Teratogens?	Agency Discretion in Regulating Mutagens, Carcinogens, or Teratogens?	Procedure for Issuing Regulations	Use of Systematic Approaches to Information Gathering, or Testing	Selected Other Regulatory Initiatives, Enforcement Efforts, or Devices
• Due to FDA's opinion that cosmetics have no significant health benefits, it is much less tolerant of any potential for injury from cosmetics • FDA is usually confronted with localised, short-term, allergy-related responses to cosmetics; long-term risks are largely unstudied.	No	No, but FDA encourages manufacturers to conduct short term mutagenesis tests	Yes	• Informal notice and comment rulemaking	FDA is not authorized to require premarket testing of cosmetics, or to require manufacturers to prove the safety of their products before marketing them. Consequently, FDA often relies on voluntary testing programs by manufacturers.	• Ingredient labels • Warning labels (e.g., in hair dyes) • Voluntary registration of products • FDA limited to post-marketing enforcement efforts (For remedies once a cosmetic is deemed adulterated or misbranded, see "foods" section)
Regulatory efforts are directed primarily at risks of microbial and chemical adulteration, and risk of disease	No	No, except in fulfilling its responsibilities to enforce animal drug, food additive, and pesticide residue regulations of FDA and EPA	Yes, except residues above FDA or EPA "tolerances" must be reported to these agencies	Notice and comment rulemaking generally	• Inspections administered by the Food Safety and Quality Service 1. Slaughter operation inspections -reliance primarily on visual inspection 2. Processing inspections -emphasis on supervision rather than individual product inspection. 3. Chemical residue surveillance - USDA conducts continuous "blind" monitoring system to analyze samples for approximately 60 different types of chemicals and pesticides regulated by FDA and EPA.	• Inspected meat and poultry may be detained, seized or condemned. Permission to operate a manufacturing or processing plant may be withheld until sanitary requirements are met. Facility may be permanently shut down, though this rarely occurs. • State inspection activities partially funded by federal government • Technical assistance available to states

Statute (date of enactment and major amendments), Agency, and Jurisdiction	STATUTORY STANDARD FOR REGULATORY ACTION		AGENCY CONCERNS IN REGULATORY ACTION
	Standard	Regulatory Decision or Action	Benefits?
FEDERAL HAZARDOUS SUBSTANCES ACT (enacted in 1960, major amendments in 1966 and 1969) • Administered by the Consumer Product Safety Commission • Regulates consumer product hazards except pesticides, tobacco products, foods, drugs, cosmetics, portable fuels, and certain nuclear materials	A. Toxic, corrosive, flammable, combustible, or irritating substances that may cause "substantial" illness from "customary or reasonably foreseeable" use B. Toys or articles intended for use by children presenting an "electrical, mechanical, or thermal hazard," or which bear or contain hazardous substances	A. Labeling hazards, or if that is inadequate, then banning hazards B. Banning such hazards	Yes - Courts have said Commission must consider the effect of the regulation on manufacturers and consumers
CONSUMER PRODUCT SAFETY ACT (enacted in 1972, major amendments in 1976, 1977 and 1978) • Administered by the Consumer Product Safety Commission • Regulates consumer product hazards except firearms, motor vehicles, tobacco products, aircraft, boats, pesticides, foods, drugs and cosmetics • Commission must defer to the regulatory authority of other agencies under the Clean Air Act, the Atomic Energy Act, and the Occupational Safety and Health Act.	A. Reasonably necessary to prevent or reduce an unreasonable risk of injury. B. Imminent and unreasonable risk of death, serious illness, or severe personal injury. C. Substantial risk of injury, or failure to comply with a safety rule.	A. Substantive safety standards regulating performance (preferably) composition and design of consumer products; banning or labeling a product. B. Seeking an injunction against an imminent hazard. C. Regulating substantial product "hazards".	Yes - Legislative history indicates CPSC should consider the effect of a regulation on the cost, utility, and availability of a product to consumers

AGENCY CONCERNS IN REGULATORY ACTION Risks	Routine, Rigorous Risk-Benefit Analysis?	Agency Emphasis on Mutagens, Carcinogens, or Teratogens?	Agency Discretion in Regulating Mutagens, Carcinogens, or Teratogens?	Procedure for Issuing Regulations	Use of Systematic Approaches to Information Gathering, or Testing	Selected Other Regulatory Initiatives, Enforcement Efforts, or Devices
A. Courts have said no precise "risk count" is necessary, but Commission should consider probability and severity of injury B. Substantial injury standard requires Commission to focus on non-trivial risks	No	Yes-An interim policy on the generic regulation of carcinogens in consumer products has been proposed. Court has enjoined its implementation due to commission's failure to comply with proper rulemaking procedures.	Yes	• Commission uses the "formal" rulemaking procedures provided for in the Food, Drug, and Cosmetic Act for regulating hazardous substances. Toys, however, may be regulated using informal notice and comment rulemaking procedures.	• Inspections of manufacturers	• Seizure of misbranded substances • Repurchase orders mandatory after banning a substance • Criminal penalties

"Reasonably foreseeable exposures" to particular hazards are estimated and given great weight.
Risk of injury has been found to be crucial to Commission's actions.
	No	Yes-An interim policy on the generic regulation of carcinogens in consumer products has been published. Court has enjoined its implementation due to Commission's failure to comply with proper rulemaking procedures	Yes	• Notice soliciting offer to develop a standard. Unless an existing federal standard is adequate to address the particular hazard, the Commission must accept an offer or develop one of its own. This becomes the proposed rule, and informal notice and comment rulemaking follow, with the opportunity for interested persons to make oral presentations.
				• Petitions to develop or amend rules may be submitted by interested persons.
					• National Injury Information Clearinghouse:
					  • hot line
					  • death certificate collection
					  • National Electronic Injury Surveillance System (NEISS) -monitors emergency room admissions and provides data for Consumer Product Hazard Index
					• Product Safety Advisory Council-recommends standards
					• Investigative hearings
					• Manufacturer notification of substantial product hazards
					• Recordkeeping by manufacturers
						• Private damage suits
						• Inspections
						• Civil, criminal penalites
						• Recall, repair, replacement of risky products. Also, refund of purchase price.

Statute (date of enactment and major amendments), Agency, and Jurisdiction	STATUTORY STANDARD FOR REGULATORY ACTION		AGENCY CONCERNS IN REGULATORY ACTION
	Standard	Regulatory Decision or Action	Benefits?
OCCUPATIONAL SAFETY AND HEALTH ACT (enacted in 1970) • Administered by the Occupational Safety and Health Administration • Regulates hazards in the workplace. Excludes authority over other federal agencies, or where those agencies exercise prior authority	A. Furnish employees a place of employment "free from recognized hazards" likely to cause death or serious harm.	A. Employer's duty under the "general duty" clause of the act.	Yes - Economic and technologic feasibility involved in determining "recognized" hazards. Courts say when viability of employer threatened, general duty standard is infeasible.
	B. "Grave danger" from exposure to toxic or physically harmful substances, or from new hazards.	B. Issuing an emergency temporary standard	Yes - Economic and market factors may enter into the agency's decision to issue an emergency standard.
	C. "Material impairment" of health of employees	C. Issuing a permanent standard	Yes - The statute specifically says permanent standards must be "feasible." • Economic infeasibility - involves massive "industry wide" disruption to challenge most standards; enforcement of some "minor" standards has been challenged successfully for lesser economic disruptions. • Technologic infeasibility - As statute is "technology forcing," such challenges unlikely to succeed, though theoretical limits on technologic feasibility exist.
NOISE CONTROL ACT (enacted in 1972) • Administered by EPA • Regulates noise and noise sources; EPA is also supposed to coordinate noise control activities with other agencies • Primary responsibility for aircraft noise control is in the Federal Aviation Administration	Protect the public health and welfare	Issuing noise control standards	Yes - Statute explicitly requires EPA to consider the costs and technology of compliance

AGENCY CONCERNS IN REGULATORY ACTION Risks	Routine, Rigorous Risk-Benefit Analysis?	Agency Emphasis on Mutagens, Carcinogens, or Teratogens?	Agency Discretion in Regulating Mutagens, Carcinogens, or Teratogens?	Procedure for Issuing Regulations	Use of Systematic Approaches to Information Gathering, or Testing	Selected Other Regulatory Initiatives, Enforcement Efforts, or Devices
Courts have said that practices other than "freakish occurrences" leading to serious injury may be dealt with under the general duty clause. Regulates risks that "reasonably" are matters of general knowledge. Under this standard, courts have said that prophylactic regulation of carcinogens is still possible: Need not wait until actual harm occurs, but harm must be serious and preferably documented by epidemiologic data. Under proposed rules regulating occupational carcinogens: • Epidemiologic data heavily weighed • Animal tests, especially if duplicated, are acceptable • "Short term" tests are given supportive value • Agency considers there to be no safe "threshold" level for exposure to carcinogens. For non-carcinogenic toxic substances, agency considers threshold levels of toxicity to exist. Epidemiologic and animal test data are weighed.	No	Yes—Generic rules on occupational carcinogens have been proposed.	Yes	• Emergency temporary standards effective on publication • Permanent standards-informal notice and comment rulemaking. Informal public hearing available on request. • Many pre-existing federal standards adopted by reference.	• Use of advisory committees is optional in issuing standards • National Institute of Occupational Safety (NIOSH) conducts research and testing, and recommends standards • "Fact-finding" hearings sometimes held. • Recordkeeping by employers	• On-site inspections of employers • Civil and criminal penalties • Agency sometimes issues enforcement "guidelines" for employers
• Statute singles out certain noise sources for regulation • EPA considers the physiologic, psychologic, and "quality of life" affects of noise	Yes	No	Yes	Informal notice and comment rulemaking. Public hearings normally held.	• Advisory committees • Recordkeeping by manufacturers • Funding for research activities	• Labeling "noisy" products • Designating certain "low noise" products for preferential purchase by the government; development of low noise products • Citizen suits • Civil, criminal penalties

Statute (date of enactment and major amendments), Agency, and Jurisdiction	STATUTORY STANDARD FOR REGULATORY ACTION		AGENCY CONCERNS IN REGULATORY ACTION
	Standard	Regulatory Decision or Action	Benefits?
TOXIC SUBSTANCES CONTROL ACT (enacted in 1976) • Administered by EPA • Regulates toxic substances, not including firearms, pesticides, special nuclear material, tobacco products, foods, drugs, cosmetics • EPA has complete descretion to use TSCA instead of other EPA administered laws; although EPA can exhort other agencies to regulate a particular substance, only in certain circumstances can it regulate substances within the jurisdiction of these other agencies	A. "Unreasonable risk" to health or the environment B. Imminent and unreasonable risk of serious or widespread injury	A. Limiting, banning, or labeling chemical hazards B. Immediate ban of a chemical hazard	Yes - statute and legislative history indicate that EPA should consider benefits, available substitutes, economic and technologic consequences of regulation. Also, approach least burdensome to industry must be used.
SAFE DRINKING WATER ACT (enacted in 1974; amended 1977) • Administered by EPA • Regulates drinking water and substances therein	A. Standards which shall protect health to the extent feasible B. Levels of contaminants which will produce no known or aniticipated adverse health effects with an adequate margin of safety C. Standards which shall be as close to the recommended maximum contaminent levels as is feasible; or which shall specify water treatment techniques that prevent known or anticipated adverse health effects to the extent feasible D. Standards regulating the odor or appearance of drinking water or otherwise necessary to protect the public welfare	A. Interim primary drinking water regulations (maximum contaminent levels or treatment techniques) B. Recommended maximum contaminant levels (MCL's) (unenforceable health goals) C. Revised primary drinking water regulations (to be issued after interim primary regulations and National Academy of Sciences report) D. Secondary drinking water regulations (not federally enforceable)	Yes - regulations are established based upon economic and technologic feasibility; also, health benefits of contaminants present in water are evaluated

6

AGENCY CONCERNS IN REGULATORY ACTION

Risks	Routine, Rigorous Risk-Benefit Analysis?	Agency Emphasis on Mutagens, Carcinogens, or Teratogens?	Agency Discretion in Regulating Mutagens, Carcinogens, or Teratogens?	Procedure for Issuing Regulations	Use of Systematic Approaches to Information Gathering, or Testing	Selected Other Regulatory Initiatives, Enforcement Efforts, or Devices
Act singles out carcinogens, mutagens, and teratogens for priority attention by EPA EPA has indicated its intention to focus on high toxicity chemicals producing irreversible or slowly reversible and debilitating effects	Possibly yes, but act is relatively new	Yes - EPA emphasizes the testing and regulation of carcinogens, mutagens, and teratogens	Yes, except act requires "appropriate action" when evidence is obtained	• Informal notice and comment rulemaking, with the opportunity for aggrieved parties to appear in person before a hearing examiner and cross-examine witnesses • Citizens may petition EPA to amend, issue, or revoke a rule	• Premarket notification given to EPA by manufacturers of all new chemicals. • Testing rules for manufacturers • Interagency Testing Committee recommends chemicals for testing • Reporting requirements for manufacturers • Funding for scientific research • Inspection of manufacturers	• Seizure of noncomplying substances • Citizen suits • Civil and criminal penalties
EPA evaluates potential "human risk" rather than determining "safety". Animal test data may be used in this evaluation, and extrapolations made from high doses to low doses. Epidemiologic data is also considered. "Threshold levels" for long term non-carcinogenic chemicals are assumed to exist, and are set at levels producing "no observed adverse effect."	No	Yes - for carcinogens EPA assumes ther are no threshold "safe" levels of exposure	Yes	• Informal notice and comment rulemaking	• National Drinking Water Advisory Council • Recordkeeping and reporting by water suppliers • Inspections of water suppliers are authorized • Grants for studying the technology for treating drinking water, and the health effects of drinking water	• States have primary enforcement responsibility • Citizen suits permissible • Notification to the public of violations

Statute (date of enactment and major amendments), Agency, and Jurisdiction	STATUTORY STANDARD FOR REGULATORY ACTION		AGENCY CONCERNS IN REGULATORY ACTION
	Standard	Regulatory Decision or Action	Benefits?
CLEAN AIR ACT (enacted in 1963, amended most recently in 1977) • Administered by EPA; states have primary responsibility to develop and enforce state implementation plans to comply with statutory standards and goals • Regulates air pollutants and their sources	A. Pollutants which cause or contribute to air pollution and which: 1. May reasonably be anticipated to endanger the public health or welfare	1. Designation of a substance as a "criteria" pollutant, leading to the establishment of a primary and secondary ambient air standard. Also governs mobile sources of pollution (e.g., motor vehicles, aircraft) requiring an emission standard, regulation of fuels and fuel additives, establishment of "standards of performance" for stationary sources of air pollution	Yes - While ambient air standards are strictly "health-based," the act frequently allows for the consideration of economic and technologic benefits (e.g., costs and technology of air pollution control)
	2. May reasonably be anticipated to result in an increase in serious irreversible, or incapacitating reversible illness	2. Designation of a substance as a hazardous pollutant (requiring a stricter standard of control)	
	B. Standards which are:		
	1. Requisite to protect the public health with an adequate margin of safety	1. Establishment of primary ambient air standards	
	2. Requisite to protect the public welfare from any known or anticipated adverse effects	2. Establishment of secondary ambient air standards	
FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT (enacted in 1947, amended by the Federal Environmental Pesticides Control Act in 1972 and the Federal Pesticide Act in 1978) • Administered by EPA • Regulates pesticides; tolerances in foods established in cooperation with the Food and Drug Administration under the Food, Drug, and Cosmetic Act	Unreasonable adverse effects on the environment	1. Considering application for EPA approval (registration) of a pesticide 2. Notice of intent to cancel registration 3. Cancellation of registration 4. Immediate suspension of registration (imminent hazards) 5. Considering whether to allow general or restricted use of a pesticide	Yes-Statute requires EPA to consider the economic, social, and environmental benefits of using the pesticide. EPA emphasizes agricultural and consumer benefits, rather than benefits to manufacturers

AGENCY CONCERNS IN REGULATOR ACTION Risks	Routine, Rigorous Risk-Benefit Analysis?	Agency Emphasis on Mutagens, Carcinogens, or Teratogens?	Agency Discretion in Regulating Mutagens, Carcinogens, or Teratogens?	Procedure for Issuing Regulations	Use of Systematic Approaches to Information Gathering, or Testing	Selected Other Regulatory Initiatives, Enforcement Efforts, or Devices
Health, environmental, economic risks are considered. Risks to humans, animals, vegetation, and "public welfare" are weighed (including an evaluation of aesthetic and structural damage caused by air pollution)	No	Carcinogen policy being developed	Yes	• Most rules can be issued after notice and comment rulemaking with an opportunity for oral presentation. • Approving state implementation plans - if state holds appropriate hearings (require an opportunity for "effective" presentation-may include a requirement for oral presentation and cross-examination) EPA need not hold an additional hearing on the state implementation plan	• Scientific Review Committee-reviews criteria pollutants and ambient air standards • National Academy of Sciences reviews auto emission standards and ambient air standards • National Commission on Air Quality-studies the feasibility and alternatives to protecting and enhancing the air quality; also examines the economic, technologic, and environmental consequences of air pollution control • Advisory committees can be used	• Transportation control plans (e.g., car pools) • Non-degradation-air cleaner than ambient air standards is not allowed to deteriorate "significantly" (specified numerically) • Non-attainment plans - allow for continued industrial growth for a limited time in areas dirtier than the ambient air standards if states use "reasonable" measures to establish "reasonable" progress in meeting ambient air standards as quickly as "practicable"
• EPA must consider the economic, social, and environmental costs of using the pesticide • EPA has established a "rebuttable presumption" against registering an oncogenic pesticide-that is, such a pesticide is considered unsafe unless proven otherwise • EPA focuses on three types of risks: a. Emergency b. Acute Toxicity c. Chronic Toxicity • For "imminent hazards" EPA must find a "substantial likelihood" of serious harm during administrative proceedings • Oncogenicity may be based upon findings in test animals	No	Yes-Agency guidelines on cancer causing substances have been issued. Cancer Assessment Group evaluates chronic toxicity risks	Yes	• Notice and comment rulemaking generally, except USDA and a Scientific Advisory Panel must be given an opportunity to scrutinize and comment on regulations	• Recordkeeping by manufacturers • Manufacturer notification of certain product hazards • Registration of pesticide manufacturers • Inspection of manufacturers • Scientific Advisory Panels review regulations	• Seizure of mislabeled or unregistered pesticides • Civil, criminal penalties • Orders involving penalties and registration may be issued after a formal adjudicatory hearing (if requested), except: a. Orders suspending the registration of a pesticide-"expedited" hearing held b. Emergency orders-may be effective immediately, followed by expedited hearings • "Stop-sale" orders may be issued to prevent continued distribution of violative products.

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APPENDIX D

INTERNATIONAL COMPARISONS OF FOOD SAFETY REGULATION*

Introduction

In order to obtain information on major regulatory principles and structures, a limited international survey was conducted with the understanding that a comprehensive survey would be infeasible. In light of the rapid progress that food safety regulation is currently experiencing, as well as the many different ways in which food safety regulation is conducted, a limited sample of organizations and countries was selected to illustrate the major international patterns of regulation with emphasis on their relevances to issues in food safety policy in the United States. The sample included:

- The United Nations' Food and Agricultural Organization, World Health Organization, Joint Expert Committee on Food Additives (JECFA) and Codex Alimentarius Commission. 1/
- The Commission of the European Communities' Scientific Committee for Food. 2, 3/
- Bulgaria, representing the general patterns followed by the member countries of the Committee for Mutual Economic Assistance (COMECON). 4/
- Japan 5/, Norway 6/, Sweden 7/, and the United Kingdom 8/ as representatives of various approaches to food safety regulation in industrialized countries.

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*Prepared by Knut Ringen, staff officer of the Institute of Medicine, National Academy of Sciences. Comments on an earlier draft by Dr. Frank C. Lu, University of Miami, are gratefully acknowledged.

Table D-1 summarizes the information obtained.

Regulatory Classifications

The organizations included in this report generally categorize hazardous substances in foods as: (1) food additives, and (2) food contaminants (or foreign substances in foods). The category "indirect additives," used in U.S. food law, is not used in the instances surveyed in this report.

None of the countries surveyed distinguishes between "natural" and "artificial" food additives. However, in a 1975 opinion on the status of food colors, the EEC's Scientific Committee for food exempted from safety testing compounds:

> "...which are in fact constituents of food and derived from coloured natural foods by purely physical processes...provided the quantities ingested do not differ substantially from the amounts likely to be ingested as a result of the normal consumption of the foods in which they occur naturally." 9/

Regulatory philosophies in Bulgaria and Norway also seem to actively encourage the development and use of additives of natural origin on the basis of not wanting to add synthetic risks to the baseline of natural risks that already exist. For instance, Norway banned all artificial colors from use as food additives on January 1, 1978. Other countries, such as the United Kingdom, explicitly reject this distinction.

All countries surveyed are either using, or developing, positive (or permitted) lists for additives. These lists may state the levels at which permitted additives are to be added to particular foods.

TABLE D-1

INTERNATIONAL COMPARISON OF FOOD SAFETY REGULATION

Country	Regulatory Classification	Regulatory Principle (Food Additives)	Concern for Special Population	Positive or Permitted List for Additives	Decision-Making Responsibility
Bulgaria	Additives/ Contaminants	Threshold/ADI levels*	Children, old and sick people, pregnant women, people with special dietary habits. No non-nutritional additives (e.g., sweeteners) allowed in children's foods	Yes (Being Refined)	Minister of Health Regionalized Implementation and Enforcement
Japan	Additives/ Contaminants	No observable risk for carcinogens Threshold ADI levels for some other risks	- No Information -	Yes	Minister of Health
Norway	Additives/ Contaminants	No observable risk	Hypersensitive reaction; High consumption populations	Yes	Director General of Health
Sweden	Additives/ Contaminants	Risk/Benefit Assessment	Hypersensitive reactions; High consumption populations	Yes	Board of Governors, National Food Admn.
United Kingdom	Additives/ Contaminants	Benefit/Risk Assessment	Not practiced - (Proposals for protecting some groups through labeling being considered)	Being Developed	Minister of Agriculture, Fisheries and Food (England and Wales), The Scottish Home and Health Department (Scotland) Department of Health and Social Services (Northern Ireland)

*ADI means Acceptable Daily Intake level

Regulatory Philosophies Governing the Regulation of Food Additives

The authority to regulate food safety is usually provided in a national food safety statute. Under the statute, it is normally an offense to sell foods containing toxic substances. The regulation of food additives tends to fall into three levels:

1. Carcinogenic Risks

Most countries will not allow additives known to pose carcinogenic risks in the food supply. When such risks are detected, the additive is usually banned. Thus, the view expressed in 1957 by the FAO/WHO JECFA generally agrees with the principle that was later incorporated into the U.S. Delaney clause:

> "The Committee believes that no proved carcinogens should be considered suitable for use as a food additive in any amount." 10/

2. Serious, But Not Irreversible Risks

For additives that pose serious risks, and that are reversible (such as a number of allergies), regulators will make concerted efforts to prevent consumption through mechanisms such as restricted distribution and information dissemination. If these risks are found to be sufficiently severe, the substances may be banned.

3. Weak or Uncertain Effects

For substances that pose a weak risk, or if the nature and level of the risk is not fully understood, a benefit assessment may be conducted to determine if the substance should be allowed in use. Benefits are thus normally considered only when the risk associated with consumption of a substance is in doubt.

Principles Used in the Assessment of Safety

Generally, every country has established an expert committee to evaluate data on the safety of substances. Principles used in the assessment of safety may be placed in three categories:

1. No Observable Risk

A number of countries will not allow additives in food if these additives have been associated with an observed health risk, especially a carcinogenic risk.

Thus, Norway promotes the use of as few additives as possible and applies this principle to the regulation of most health risks associated with food additives. On this basis the number of additives used in foods has been reduced by 50% over the past 15 years, including a phased-out ban of nitrites from most foods announced in 1973.* Most countries, however, follow this strict principle only in the case of carcinogenic risks.

It is important to realize the difference between absolute safety and no observed risk. The latter concept relies on the state of the art of scientific methods to detect risk as the criteria for determining whether a substance should be allowed in use or should be banned from use.

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*This is in general agreement with an overall vigorous policy in agriculture and nutrition, where the government is seeking to change the national diet by changing the foods that are available in the market. 11, 12/

2. Threshold Levels and Acceptable Daily Intake (ADI)

In determining safety, a number of organizations and countries rely on combinations of observed risk and consumption levels. Thus, the EEC's Scientific Committee on Food states in relation to materials that come into contact with foodstuffs:

> "To assess whether a substance is harmful to man it is necessary to have information on its toxicity, on the quantity of the substance migrating into food and its daily intake by man." 13/

The WHO/FAO JECFA also advocates the establishment of ADI's for non-carcinogenic food additives and for contaminants. The establishment of ADI's requires an understanding of the full profile of the acute and chronic toxicity of a substance. In assessing the safety of a food additive, the potential daily intake is compared to the corresponding ADI. Potential daily intake is determined on the basis of the additive's permitted level of use in various foods, and the level of consumption of such foods. Many countries, such as Bulgaria, require the use of ADI's in risk determination for both additives and contaminants, and almost all countries rely to some extent on ADI figures for the regulation of contaminants.

3. Risk-Benefit Assessment

Among the countries surveyed in this overview, Britain and Sweden rely on informal methods of risk-benefit assessment to determine the acceptability of substances in foods. In both countries a case-by-case approach is used where Committees agree on the relative risks and benefits associated with consumption of a substance.* Their approaches to the regulatory decision-making, however, are significantly different:

Britain begins the process of regulatory evaluation by questioning the "need" for the substance — that is, its benefit. If no benefit is ascertained, the additive will not be allowed in use. If a benefit is ascertained, the regulators assess the risk of the substance by evaluating toxicologic data and consumption figures. The risks and benefits are then weighed against each other. Benefits include health consideration, special dietary needs of certain subpopulations, technical improvements in manufacture, processing and storage, and economic benefits to the consumer. In Britain (as in several other countries), a new food additive will be permitted only if it is at least as effective, and poses no greater hazard to the health of the consumer, than the additives that are already available.

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*As suggested in Chapter 9 of this report, a regulatory system that is flexible and diverse can only function when the regulatory agency has a certain degree of autonomy. In Sweden, an independent agency, the National Food Administration, has a 12-member board comprised of representatives of various major political interests. It is thus politically autonomous within Sweden's system of corporate democracy. 14/ In Britain, the relatively large autonomy of the executive branch (compared to the U.S.) stems from unique historical circumstances particularly in relation to the origin and role of the civil service corps. 15/

Sweden begins the regulatory process by ascertaining the risk of a substance and its daily intake. If the risk is judged to be excessive, the substance is banned. Otherwise, a benefit assessment is conducted. If a known risk is associated with a substance only substantial health benefits may justify its marketing (e.g., fortifiers, antitoxidants), and even then the use is limited to ensure that consumption will not exceed the established ADI level. Also in Sweden the types of risks and benefits that are considered have not been established formally, and may vary from substance to substance.

Special Populations

Regulatory patterns seem to demonstrate increasing concern for populations that may be particularly vulnerable to a substance. Recent regulations attempt to protect marginal population groups to whom a substance poses a special risk either because of unusually high consumption levels or because of special susceptibility to the health hazards of a substance. ADI levels are increasingly being established at the level at which the substance is judged to pose no known risk to these population groups. Thus, in the case of Bulgaria, emphasis is placed on protecting children, pregnant women, old and sick people, and people with special dietary habits or needs. However, determination of the degree to which marginal populations should be protected remains unclear. This determination would depend on the nature of the hazard associated with the substance, its toxic potency, and the type and extent of the population exposure. Thus, while current regulatory patterns are not uniform in the protection of special populations, they do suggest a trend towards greater protection.

Information Dissemination in Regulation

Current trends in food safety policy also indicate an increasing use of information and/or warnings to guide the consumer in the consumption of substances that may pose some risk. This approach is used where the health effect is nonlethal and reversible, such as substances that may cause allergic reactions. This approach may also be used in the regulation of natural constituents of foods that are judged to pose some hazard. Increasingly, regulators are targeting this information towards special population groups such as high level consumers, in order to help them to reduce their levels of consumption to within the established ADI levels. Information campaigns have been used extensively to limit consumption of fish from waters contaminated with mercury, and at least in Sweden, this approach appears to have worked.

The use of warning labels on food containers is generally discouraged, but informational labeling is commonly used. The standardization of codes to identify colors and additives promoted by the Commission for the European Communities is increasingly gaining acceptance within and also outside the Community. The Swedish attempt to coordinate food safety regulation with information provided through the health services indicates that an effective labeling approach may require a mechanism to help individuals understand how their specific health needs relate to the information on food labels.

Who Decides in Regulation?

In most countries, food safety regulation is located in the national health administration (e.g., Japan, Norway and Bulgaria), whereas in the unique case of Sweden, food safety regulation is conducted by an autonomous agency. With the exception of Norway, the responsibility for food safety regulation is vested with a political authority (usually the Minister of Health). In Norway, the Director General of Health, a civil servant, is responsible. Bulgaria displays an interesting system of regionalized food safety regulation where regulatory authority to some extent is limited to different levels of need (i.e., local, regional, and national). Other countries (Norway and Sweden) also seem to rely on local health authorities to take responsibility for local needs. This approach suggests a desire to ensure that food safety regulation is as flexible as possible and responsive to local needs, particularly in regard to the regulation of hazards associated with environmental contamination (such as mercury).

International Cooperation in Food Safety

Interest in international cooperation in food safety regulation has been growing steadily since the establishment of the FAO/WHO Joint Expert Committee on Food Additives in 1955 and the Codex Alimentarius Commission in 1963. In response to a recommendation of the 1972 United Nations Conference on the Human Environment, the FAO/WHO Joint Food Contamination Monitoring Program was established. As the concern for food safety has increased, and with the growing complexity of ensuring food safety, countries are intensifying the search for data and analyses. With international trade increasing, there is also a desire to achieve greater international consistency in national regulatory standards, so that fairness in the trade of foodstuffs is ensured, and so that regulatory standards are not used to promote national barriers to trade. 16/ The international organizations are facilitating cross-national transfer of information both on the potential risks of substances in foods, and on different methods and standards of regulating food safety. International cooperation has proved particularly useful to small nations that do not have the resources or capabilities to engage in extensive research of their own.

U.S. Participation in International Food Safety Activities

The United States, through its government, universities, research organizations and industry, is the world's largest source of data related to food safety. Because of the vast amount of information generated domestically, U.S. reliance on international programs in food safety has been limited. The U.S. Food and Drug Administration is actively involved in FAO/WHO programs, as well as in a Tripartite Toxicology Committee established at the agency-head level involving the United Kingdom, Canada and the U.S. FDA is indirectly represented on certain other international bodies, such as the International Agency on Research on Cancer (IARC), where the National Cancer Institute represents FDA.

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APPENDIX E

The Decision Framework: An Application to Saccharin

As a hypothetical example that illustrates the use of the decision framework in Figure 4-2, let us consider saccharin, based partly on the evidence summarized in Chapter 3, as well as in Part 1 of this report.

Using the decision framework as shown in Figure 4-2, let us consider saccharin (a) in toothpaste, (b) in soft drinks and (c) as a self-added sweetener.

(a) Actual consumption of saccharin while brushing one's teeth is so small that insignificant risk is assumed to exist. A decision is reached in (E) "Permit use of saccharin in toothpaste."

(b) For saccharin in soft drinks health risks exist (C); there is not a less risky noncaloric sweetener (D); the risk may be concentrated in children and pregnant women (G); these groups may be judged not to receive commensurate benefits (O), so they should be restrained from use as much as feasible* (T). Low risk consumers

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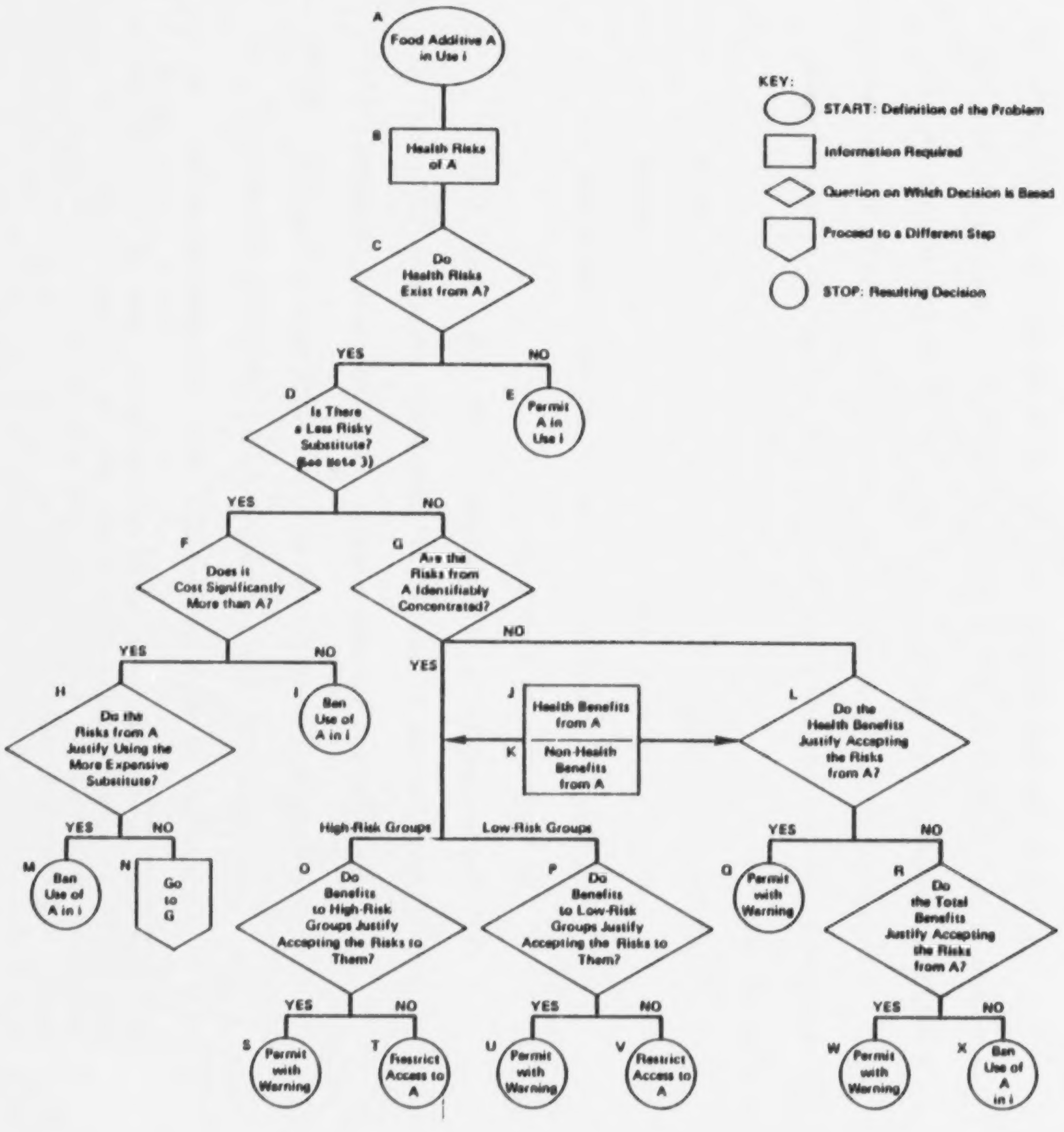
*It should be noted that some forms of restraint, such as treating diet soda as if it were medicine or alcohol, may be incompatible with the nature of the product. If the risk were differentiated between the sexes, differential market access may be socially unacceptable. On the other hand, some forms of restraint might be appropriate. For these reasons, we choose to use "restrict" rather than "ban" in the cases where population groups are considered separately.

Figure 4-2. An illustration of a decision process for food additives.


A
Food Additive A in Use i
B
Health Risks of A
C
Do Health Risks Exist from A?
YES
NO
D
Is There a Less Risky Substitute? (See note 3)
E
Permit A in Use i
YES
NO
F
Does it Cost Significantly More than A?
G
Are the Risks from A Identifiably Concentrated?
YES
NO
H
Do the Risks from A Justify Using the More Expensive Substitute?
I
Ban Use of A in i
YES
NO
J
Health Benefits from A
K
Non-Health Benefits from A
L
Do the Health Benefits Justify Accepting the Risks from A?
YES
NO
M
Ban Use of A in i
N
Go to G
High-Risk Groups
Low-Risk Groups
O
Do Benefits to High-Risk Groups Justify Accepting the Risks to Them?
P
Do Benefits to Low-Risk Groups Justify Accepting the Risks to Them?
YES
NO
Q
Permit with Warning
R
Do the Total Benefits Justify Accepting the Risks from A?
YES
NO
YES
NO
YES
NO
S
Permit with Warning
T
Restrict Access to A
U
Permit with Warning
V
Restrict Access to A
W
Permit with Warning
X
Ban Use of A in i
KEY:
START: Definition of the Problem
Information Required
Question on Which Decision is Based
Proceed to a Different Step
STOP: Resulting Decision

NOTES FOR FIGURE 4-2

1. An ellipse represents the starting point of the analysis. Rectangles represent informational inputs to the decision process. In this example, the required information is the scientific or technical evidence on the existence, magnitude, and distribution of the health risks; the health benefits; and the nonhealth benefits, attributable to the consumption of the additive in a specific use. Diamonds represent decisions from which the subsequent path is determined by the answer to the question. Pentagons represent instructions to go to a different step in the decision-making process, and circles represent end points indicating the appropriate regulatory policy.

2. This illustration can be expanded and modified. For example, the consideration of risk groups at O and P can be expanded to include three or more categories.

3. Benefits are an integral part of the concept of a substitute. The term substitute, as used in D, F, and H, refers to a substance essentially similar to the additive (A) in all relevent properties except risk and cost.

4. This decision process can be modified to apply to foods with contaminants, naturally-occurring toxic substances, etc.

might realize benefits which justify accepting the risk (P), so they should be permitted to consume saccharin in soft drinks, but should be educated and warned that some risk exists (U).*

The decision framework illustrated in Figure 4-2 is suited for dealing with deliberately added substances, for which the policy question is: should the additive be permitted (i.e. in which uses for which consumers). The question of how much of the additive to allow in the permitted uses is not raised here; if this is to be a public policy decision a more explicit examination is required of the trade-offs between the impacts of cost changes, reduced consumption benefits, and health risks.

To consider either a raw agricultural commodity, including its "natural constituent," or a "contaminant," such as mercury or aflatoxin, but not substances deliberately added to introduce or amplify some characteristic of the food, some major modifications of the decision framwork are necessary. For example, there may be no health or nonhealth benefits to be derived from consuming the constituent or contaminant itself. Nor is it always appropriate to consider substitutes for the risk-producing substance. Instead, consideration must be given the categories of foods for which the substance is a potential safety problem: what are the substitutes for foods posing the risk of excessive contamination, and what potential health and nonhealth benefits would be given up by restricting consumption of these foods.

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*These policies are consistent with the recommendations in Chapters 9 and 10.

APPENDIX F

RISK ESTIMATES [TO HUMANS FROM ANIMAL TESTS]

A chemical that has been associated with an increased cancer incidence in bioassays of laboratory animals is likely to be a carcinogen in humans. Extrapolation to humans of cancer incidence in animals is necessary to quantify the expected degree of risk for humans that are exposed to concentrations of the chemical that differ from those in the bioassays of animals. This extrapolation procedure consists of two basic steps:

1. within the test animal species, extrapolation of the experimental results of tests performed at high exposure or dose levels to much lower exposures in animals, which correspond to human exposures; and
2. extrapolation of these estimated risks for animals at low doses to the risks for humans at comparable levels.

The first step in this process requires the assumption of some biological model, which implies a mathematical rule that relates the dose level of a particular carcinogen to an ob-

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* National Research Council, Institute of Medicine, Committee for a Study on Saccharin and Food Safety Policy, Saccharin: Technical Assessment of Risks and Benefits, pp 3-61 to 3-69. Washington, D.C.: National Academy of Sciences, 1978.

servable response, e.g., the occurrence of a particular type of tumor at any time within the animal's natural lifespan or lifetime for the duration of the study. This assumption is normally required since the animal studies are conducted at much higher exposure levels than are commonly found for human exposures. These high exposure levels must be used to obtain measurable results with a limited number of animals. At dose levels that correspond to common human exposures, several thousand animals would be needed to estimate the increased carcinogenic risk in humans.

Many theoretical dose-response models of carcinogenesis have been proposed, each of which leads to a particular mathematical form for this dose-response relationship. All theories have one concept in common: that there is no known uniform threshold dose below which any carcinogenic response is impossible for all individuals at risk. Even if thresholds do actually exist, it is scientifically impossible to measure them or to prove their existence. In addition, the assumption of one uniform threshold for heterogenous groups is unrealistic. It is much more likely that each member of the population has an individual threshold level which is some complex function of unique biochemical and physiological composition. A further argument against use of threshold models for the estimation of attributable risk is that the environment contains many carcinogenic agents and that the particular chemical in question may be acting additively over and above this "background." Therefore, since tumors do appear spontaneously in a control population, the threshold, assuming it does exist, has probably already been exceeded by the environmental background. Craig and Miller (1974), in a review of 151 dose-response curves, found only one to be inconsistent with the no-threshold hypothesis.

Some of the more commonly used mathematical extrapolation modes are the following:

The probit model is derived from the assumption that each member of the population has his own tolerance level for the chemical, below which there will be no response and above which the subject will respond. These tolerances are further assumed to vary among members of the population and to follow a log-normal probability distribution. Mantel and Bryan (1961) have suggested use of a modification of this model for extrapolation of carcinogenesis bioassays from high to low doses. Since the tolerance distribution for the homogenous laboratory animal population should have a smaller variation than that of the heterogenous human population, they suggest that the risk extrapolation be based on a model with a more shallow slope than that observed in the bioassay. This shallow slope should be no greater than the average true slope over the extrapolation range. A slope of one probit per 10-fold change in dose is commonly used for this Mantel-Bryan extrapolation.

The single-hit, or single-event, model is derived from the assumption that cancer starts in a single cell as the result of some random event, or "hit", which produces an irreversible change in the cell's DNA. It is further assumed that the probability of this event, attributable to the carcinogen in question, is proportional to the exposure level.

The multi-stage model (Crump *et al*., 1976), a generalization of the single-event model, is derived by assuming that the carcinogenic process consists of some unknown number of stages that are required for cancer expression. The probability of at least one of the transitions from one stage to another is assumed to be a property of the particular carcinogen in the same manner as the single-event model.

Other models, such as the log-logistic and multi-hit models (Food Safety Council, 1978) have also been proposed, but the three models described above produce a range of extrapolations that would be obtained by most other models. Models of dose-response based on the actions and reactions on in-vivo chemical and physiologic processes have also been proposed (Gehring and Blau, 1977). These are determined by a series of differential equations corresponding to multicompartmental models of the chemical processes within the body that correspond to the internal fate of the chemical carcinogen.

The difficulty with using any of these dose-response models for high- to low-dose extrapolation purposes is their similarity over the observable response range, 5% to 95% response rates, contrasted with their dissimilarity in the range of very low response rates (Table 3-7).

Although all three models are similar in the observation range, the lower part of the table shows that extrapolation to exposure levels that are expected to give very low response rates is highly dependent upon the choice of mathematical model. The upper part of Table 3-7 shows that three of the most commonly used models differ by very little over a 256-fold dose range. At a dose that is 1/1000 of the 50% response

TABLE 3-7

Expected Response Rates as a Function of Dose for Different Dose-Response Models[a]

Relative Dose	Log Normal,%	Log Logistic,%	Single Hit,%
16	98	96	99+
8	93	92	99
4	84	84	94
2	69	70	75
1	50	50	50
.50	31	30	29
.25	16	16	16
.125	7	8	8
.063	2	4	4
0.01	.05	.4	.7
0.001	.00035	.026	.07
0.0001	.0000001	.0016	.007

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[a] Data from USDHEW, 1971.

dose, the single-hit model gives an estimated response rate that is 200 times as large as the log-normal model. The fact that a limited animal bioassay that is conducted at dose levels high enough to give observable response rates cannot discriminate among these various models and the fact that these same models are substantially divergent at lower dose levels provides the major uncertainty for high- to low-dose extrapolation.

When using a model that is fit to the experimental result and is then used for extrapolation, it is assumed that the dose-response relationship observed at these high-dose levels will continue to hold throughout the entire spectrum of exposure levels. This assumption has been questioned by toxicologists and other health scientists. The effective exposure level, the amount of the carcinogen actually reaching the target cells and molecules, may well be some complex function of the absorption, distribution, biotransformation, and excretion of the host. Each factor may depend upon and influence the level of the carcinogen to which the animals are exposed. The in-vivo mechanisms that relate environmental chemical exposure levels to the levels that reach the target cells cannot be adequately quantified; thus, proportionality between the environmental exposure level and the effective exposure level is commonly assumed. This assumption is no doubt an oversimplification of the true relationship; however, without information on metabolic pathways, activation and deactivation systems, and other pharmacokinetic considerations, it is generally accepted.

The second step in the human risk assessment process is extrapolation from laboratory animals to humans. For compounds that are known carcinogens in animal models as well as in humans, significant differences can be observed both among species and among various strains within species. Some animals are hypersensitive while others are refractory to the effect of the same chemical carcinogen. In some cases, differences in site specificity can be observed among various strains and species. Many of these differences can be related to metabolic factors, i.e., the compounds are metabolized through pathways that generate an ultimate toxicant or carcinogen. This metabolic activity is focused in specific organs, thereby increasing the probability of a toxic response within that organ. Within the framework of metabolism, the rates of biotransformation are also quite critical. The relative rates of activation and inactivation are important factors in determining the duration of exposure of target molecules to the carcinogenic substance. Systemic distribution may play a vital role, since the ultimate toxicant may be generated in one organ and redistributed to another to exert its toxic effects. Repair mechanisms and their rates also affect the ultimate manifestations of the lesions. If the rate of repair is relatively fast, one can expect that far more agent is necessary to produce irreversible biochemical lesions that lead to clinical manifestations. Conversely, when rates of repair are slow, relatively small quantities of an agent may be required to elicit a toxic syndrome such as cancer. Routes of excretion and rates of elimination are also vital in removing the toxicant or carcinogen from the locus in which it can combine with the target receptors.

The National Academy of Sciences (1975) has recommended that carcinogenicity testing be conducted in more than one species and that the results obtained with the most sensitive species be applied to human populations. Adjustments for "equivalent exposure levels" between animals and humans must be made. This conversion process should depend upon the routes of exposure, possibly different, for the animals and humans, information on comparative metabolism of the chemical compound, and information on the similarities and dissimilarities of all relevant biochemical and physiological parameters of the two species. When this type of information is unknown, a simple proposed conversion rule can be used. This rule is based on the assumption that the locus of action for any chemical is on some, perhaps unknown, receptor. It further assumes that different mammalian species exhibit essential similarities except for size. Accordingly, it follows that any appropriate surface area in an organism will be approximately proportional to the 2/3 power of its weight (USDHEW, 1976). This "surface area rule" can be mathematically stated for any two species as:

$$\frac{\text{dose}_1\ (\text{mg/day})}{\text{dose}_2\ (\text{mg/day})} = \frac{w_1^{2/3}\ (\text{mg})}{w_2^{2/3}\ (\text{mg})}$$

If it is also assumed that the food or air requirements for different species are dependent upon surface areas, then conversion between species is direct when exposure is given in terms of concentrations in the food or drink (Mantel and Schneiderman, 1975). An additional conversion rule is obtained from standard toxicological methodology (USDHEW, 1959), which equates dose levels on a milligram of dose per kilogram of body weight basis. These rules apply when the exposure levels are given as dose per unit of time, i.e., "dose rates". When human exposure is constant, or nearly so, over an entire lifetime, the results of chronic, constant exposure in lifetime experiments with animals may be directly extrapolated without any corrections for length of exposure. An approach based on total lifetime exposure per unit of body weight has also been used to equate species-to-species exposure levels (NAS, 1974). In a recent comparison of experimental results in animals and epidemiologic results in humans, these species-to-species extrapolation methods proved to be uniformly better than any other (NAS, 1974).

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APPENDIX G

DISCUSSION OF SACCHARIN OPTIONS

by

Fred P. Abramson (Panel 1) and Richard L. Hall (Committee)

Chapter 10 of this report (Part 2) summarizes the scientific findings on saccharin published earlier by the Study Committee (Part 1)*. Based on these findings, we present a discussion of options for regulating saccharin and possible outcomes. This appendix provided the basis for options 1 through 8, presented in Chapter 10.

Saccharin and saccharin-containing products were freely available until 1977. In April 1977, the Food and Drug Administration proposed to ban saccharin for most uses. However, saccharin continued to be marketed with a warning label under provisions of the Saccharin Study and Labeling Act. These three means of managing the availability of saccharin and other options that suggest themselves are included among seven options that are discussed in this section. For each option a "rationale" of a person who would advocate selection of that option is described. Thus, the rationale is a summary explanation of the reasons for which an individual might prefer a specific option. Other individuals may advocate a different option and have a different rationale to substantiate the choice. The resultant risks and benefits (outcomes) for society, should the option be selected by policymakers, are described for each option.

The options are in no sense recommendations since selection of a policy regarding the availability of saccharin must rest ultimately with elected officials and government agencies.

Four options involve the prohibition of saccharin as a direct food additive (Options A thru D). Option A calls for a total prohibition; Option B would permit use of saccharin in dentifrices and drugs but not as a tabletop sweetener; Option C permits its use as a drug, available either over the counter or by prescription; and Option D permits sales of packaged saccharin for use only as a tabletop sweetener.

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* National Research Council/Institute of Medicine, Committee for a Study on Saccharin and Food Safety Policy. Saccharin: Technical Assessment of Risks and Benefits. Washington, D.C.: National Academy of Sciences, 1978.

Under Options E thru G saccharin would be permitted as a food additive under regulation, e.g., by prohibiting sales to minors (E); with labeling, as is currently required by the Saccharin Study and Labeling Act or with similar restrictive label information (F); or with no restriction as before the FDA proposed a ban (G).

OPTION A: COMPLETE BAN

Restrictions:

The sale and use of saccharin for any purpose would be prohibited.

Rationale

Individuals who select this option would believe that all conclusive scientific data support the risks and that the potential hazards of saccharin use outweigh any probable (though undemonstrated) benefits in any segment of the population and for any product.

Risk and Benefit Outcomes

Since there would be no exposure to saccharin after a complete ban, there would be no increment in risks of bladder cancer due to continued use of the substance.

Because no alternative non-nutritive sweetener is currently accessible, there might be some reversion, of unknown extent, by some users of saccharin, to the use of caloric sweeteners. The health consequences of such reversion are unknown. Furthermore, less palatable dentifrices and some drugs that are less palatable, convenient, or stable would be marketed.

Discussion

It is difficult to assess the increased risk that might occur should consumers revert to the use of sugar in the absence of saccharin or an alternative non-nutritive sweetener. Although overconsumption of caloric sweeteners can lead to obesity, which is associated with increased mortality and morbidity, there is no evidence to indicate the extent to which people would replace saccharin with sugar or overuse sugar, or, if such occurred, how many persons would become obese thereby placing themselves at increased risk.

OPTION B: BANNED FROM FOOD ONLY

Restrictions

Saccharin would be prohibited as a direct food additive or as a table-top sweetener but would be permitted for use in dentifrices and drug formulations.

Rationale

Persons selecting this option would believe that the potential hazards of saccharin use in foods outweigh any probable (but undemonstrated) benefits for any segment of the population, but that the amount of saccharin consumed in dentifrices and drugs is very small with correspondingly small risks; and The benefits of having more palatable dentifrices to encourage proper use and more palatable, convenient, and stable drugs outweigh the probable risks from the use of such saccharin-containing products.

Risk and Benefit Outcomes

Since saccharin would be permitted in dentifrices and drugs, there would be no effect on the present availability and use of such products. There would be an unknown but probably very small increase in risk of bladder cancer as a result of continued use of saccharin in drugs and dentifrices.

Because food products containing saccharin would not be available, there might be some reversion, of unknown extent, by some users of saccharin to the use of caloric sweeteners. The health consequences of such reversion are unknown.

OPTION C-1: SACCHARIN AS A DRUG PRESCRIBED BY A PHYSICIAN

Restrictions

Saccharin would be permitted in dentifrices, drugs, and by physician's prescription as a drug product for use by persons with medical need for non-nutritive sweeteners. It would be prohibited as a general additive to food.

Rationale

The rationale for those who would select this option is that the risks of having saccharin widely available in foods outweigh any probable benefits, but that physicians should be permitted to prescribe saccharin for specific individuals to manage such conditions as diabetes and to control body weight.

Risk and Benefit Outcomes

Implementation of this option would result in greatly reduced exposure of that segment of the population with the smallest prospect of receiving health benefits.

OPTION C-2: SACCHARIN AS AN OVER-THE-COUNTER DRUG

Restrictions

Saccharin would be available for use in dentifrices, drugs and as an over-the-counter drug product for use by persons with a medical need for a non-nutritive sweetener. It would be prohibited as a general additive to food.

Rationale

Those who would choose this option would believe that most individuals should be permitted to exercise their judgment in seeking the possible benefits of saccharin in weight maintenance, dietary management of diabetes, and obesity reduction, despite the potential hazards.

Risk and Benefit Outcomes

There would be some increased risk of bladder cancer due to the use of saccharin, but probably substantially less risk than under the options described below under which saccharin would be permitted as a food additive. Saccharin would be available as a food sweetener that could be purchased at drug counters.

The rationale for both Options C-1 and C-2 assumes that the amount of saccharin consumed in dentifrices and drugs is very small and that the risks are correspondingly small. The benefits of having more palatable dentifrices to encourage proper use and more palatable, convenient, and stable drugs outweigh the probable risks.

Among the risks and benefits of both Options C-1 and C-2 is the lack of effect on the present availability and use of saccharin-containing dentifrices and drug formulations. Since food products containing saccharin would not be available there might be some reversion of unknown extent by some users to the use of caloric sweeteners. As stated before, the health consequences of such reversion are unknown.

Discussion

To be approved as a drug, saccharin must meet requirements for proof of safety and efficacy unless specifically exempted from doing so.

OPTION D: SACCHARIN FREELY AVAILABLE EXCEPT AS A FOOD ADDITIVE

Restrictions

Saccharin would not be permitted as a food additive but would be permitted in dentifrices, drug formulations, and as a tabletop sweetener that could be purchased in food stores.

Rationale

The rationale of those who would select this option is that the amount of saccharin consumed in dentifrices and drugs is very small and that the risks are correspondingly small. The benefits of having more palatable dentifrices to encourage proper use and more palatable, convenient and stable drugs outweigh the probable risks.

They would also believe that the risks of having saccharin widely available in foods outweigh any probable benefits, but that saccharin should be accessible to specific individuals who may derive benefits in dietary management of diabetes and weight reduction or maintenance.

Use of saccharin as a tabletop sweetener permits most of the conscious choice uses. Thus those at greatest risk could limit their intake knowledgeably, rather than be exposed to unknown amounts that have been added to food products.

Risk and Benefit Outcomes

Since food products containing saccharin would not be available, some users of saccharin might revert to the use of caloric sweeteners, neither the extent nor the health consequences of such reversion are known.

There would be some increased risk of bladder cancer due to the use of saccharin in tabletop sweeteners, but probably substantially less risk than if saccharin were permitted as a food additive.

The possible benefits of saccharin use would be retained for those who choose to use saccharin as a tabletop sweetener.

Discussion

Prohibiting the use of saccharin as a direct food additive and requiring a purposeful decision to use it as a tabletop sweetener should reduce the use of saccharin and exposure generally. Only about 25 percent of saccharin is currently used as a tabletop sweetener. As a packaged or bulk sweetener saccharin might still be classified as a food and as a food additive. Consequently, exemptions to existing statutes and regulations would be necessary to make it available. The availability of low-calorie, unsweetened foods to which saccharin could be added would permit some persons to have access to the potential health benefits and perceived benefits that are provided by saccharin-containing products.

A variation on Option D would permit saccharin in tabletop sweeteners only but not in dentifrices, foods, or drugs. This would leave the determination of saccharin consumption to the conscious, deliberate choice of the individual.

OPTION E: RESTRICTION OF AVAILABILITY OF SACCHARIN-CONTAINING PRODUCTS

Restrictions

Saccharin would be permitted as a food additive, but efforts would be made to implement restrictions that would discourage the purchase and consumption of saccharin-containing products by persons at greatest risk.

Rationale

Persons selecting this option would believe that warning labels, logos, and brochures are inadequate to permit effective management of risks, thereby necessitating the imposition of restrictions that would limit access to saccharin-containing products. If controlled distribution and restrictive use of labels direct saccharin-containing products to those for whom potential benefit is largest and discourage use by those at greatest risk, then possible benefits could accrue. Adults should be permitted to decide for themselves whether to use such products.

Risk and Benefit Outcome

There would be no effect on the present availability and use of saccharin-containing dentifrices and drugs.

Because efforts would be made to restrict sales of foods and beverages containing saccharin to persons at least risk, some unknown but probably small reduction in overall risk of bladder cancer would result compared to options which would permit more general availability of saccharin-containing products.

Saccharin-containing products would be easily accessible, but there might be some reversion to the use of caloric sweeteners by some saccharin users.

Discussion

This option provides for the reduction of exposure for particular groups of individuals who might be at greater potential risk of cancer caused by saccharin consumption. These groups are: males of all ages and young persons (because carcinogens are believed to cause cancer after a long latent period, which suggests the possible desirability of delaying the beginning of saccharin consumption). Also women of childbearing age might be well advised to avoid saccharin consumption since lifetime exposure of rats beginning in utero, produced significantly enhanced incidence of bladder cancer in male offspring. Although there is no evidence that male offspring of women who ingest saccharin during pregnancy are at greater risk, it would be consistent with current scientific concepts to believe that the experience in laboratory animals may be extrapolated to humans.

The number and combinations of means by which specific groups would be limited in their exposure to saccharin are confined only by the imagination. Certainly education, warning labels and logos would be required to inform males and women of childbearing age of the increased risk. Restrictions could be implemented to exclude uses other than management of diabetes, obesity, etc., thereby emphasizing use among those who might obtain the potential health benefits. Children would be less exposed if sales were prohibited in school cafeterias, vending machines, or to minors generally. Sales might be permitted only at drug counters rather than in food stores or only in the dietetic section of such stores. Saccharin might be permitted in some foods and beverages but not in others to reduce the amount consumed. Limitations on the amount of saccharin that is permitted in soft drinks, which would necessitate the addition of nutritive sweeteners to provide the desired sweetness, would result in a low calorie rather than no calorie drink and would reduce the amount of saccharin ingested.

It would be useful to monitor consumption patterns to determine the effectiveness of such restraints.

Reduced exposure would result in reduced risk, moreover, since the option provides for the continued use of saccharin as a food additive, those persons for whom saccharin-containing products have potential or perceived health benefits would have such products available to them. Thus, children whose parents provided them with saccharin-containing foods as part of a diabetic or weight control diet would still have the potential benefits available to them.

OPTION F: SACCHARIN GENERALLY AVAILABLE WITH A WARNING LABEL

Restrictions

None except that saccharin and saccharin-containing products would be sold with a warning label or logo.

Rationale

Individuals selecting this option would believe that the perceived and potential health benefits of saccharin appear to be greater than the low possible risks that would result if this proven but weak animal carcinogen were made available as a food additive. Furthermore, they would believe that there is little point or utility in attempting to restrict use or distribution of saccharin-containing products; that warning labels, logos, and information circulars are adequate to inform people about the risks; and that people should be permitted to judge risks and benefits for themselves and their families. In view of the uncertainties regarding the degree of risk associated with saccharin use, there may be little justification for restricting the availability more than suggested in this option.

Risk and Benefit Outcomes

Since there would be no imposed restraints on distribution or consumption, both the risks and benefits of saccharin would be widely available.

The continued availability of saccharin could lead to between zero and 3,000 additional cases of bladder cancer and between zero and 1,000 deaths due to bladder cancer per year in males in the United States. The risk may rise as consumption rises particularly by younger age groups experiencing longer exposure.

An unknown incidence of death and disease that is related to obesity might be avoided if some people use saccharin to reduce intake of excessive calories.

Discussion

If saccharin is permitted as a food additive but its packaging bears a label warning of its carcinogenicity, we speculate, based on the experience with the cigarette warning label, that consumption patterns will be affected very little and that the potential hazard will be the same as if there were no label. We speculate also that those who use the products despite the labels may be more anxious about such use and that the perceived benefits will be reduced somewhat thereby. However, since saccharin-containing products would remain generally available, there would be no loss of potential health benefits.

If saccharin-containing products were to be marketed as they were prior to passage of the Saccharin Study and Labeling Act in 1977 (Option G), the possibility exists, as stated above, that there would be perhaps 3,000 additional cases of bladder cancer in males per year in the United States. This estimate was obtained from the one positive epidemiology study reflecting past use which was conducted in 1977. Other possibilities are that in the future there would be no cases, an intermediate number of cases (10's to 100's), or many more than 3,000 cases if the maximal effects of the increasing trend toward saccharin consumption are not apparent at the present time. Although most scientists agree that a demonstration of carcinogenicity of a substance in laboratory animals means potential carcinogenicity of that substance in humans, there is no generally accepted method for estimating the number of cases of cancer that will occur in humans. Thus, there is no reliable way to confirm or deny any of the possible estimates of cancer incidence in humans as a result of continued saccharin use although various extrapolations of animal data are consistent with the epidemiologic studies.

OPTION G: FREE MARKETING OF SACCHARIN

Restrictions

None

Rationale

The rationale for those who would select this option is that perceived and potential health benefits of saccharin appear greater than the low possible risks of using this proven but weak animal carcinogen as an additive.

Restraints on use, distribution, or labeling are needless or useless, and use or non-use of saccharin is a judgment best left to the individual.

Risk and Benefit Outcomes

Since there would be no imposed restraints on distribution or consumption, both the risks and benefits of saccharin would be widely available.

The continued availability of saccharin would lead to between zero and 3,000 additional cases of bladder cancer and between zero and 1,000 deaths due to bladder cancer per year in males in the United States. The risk may rise as consumption rises particularly in younger age groups experiencing longer exposure.

An unknown incidence of death and disease related to obesity might be avoided if some people use saccharin to reduce intake of excessive calories.

Discussion

Under Option G, with no restriction on the availability of saccharin, the potential health benefits of saccharin use and the perceived or psychological benefits would be retained. The potential benefits include the use of the substance to provide sweetness without calories or carbohydrates in the diets of diabetics, those who wish to maintain or reduce their body weight, and others on special diets.

GENERAL DISCUSSION

There is no scientific evidence that permits objective assessment of the possibility that the potential health benefits of saccharin are realized. However, many persons believe there are benefits to the use of saccharin. Although practicing physicians have expressed opinions favoring the use of saccharin products by their patients, scientists who have examined the relevant data cannot determine whether or not they provide evidence that there is an effect in weight control or other measurable parameters. Although many scientists agree that definitive data to prove or disprove benefits do not exist, some scientists have intuitively interpreted the data to show benefits or no benefits. Those who hold that there are no benefits can make a simple risk-benefit assessment—saccharin is a carcinogen of low potency, but has no benefits and, therefore, has no place in the human diet (i.e., Option A). Those who believe that there are benefits (for those who use the substance instead of, rather than in addition to, caloric sweeteners) can say that the potential benefits should be weighed on the scales of risks and benefits along with its low potency carcinogenicity (Options B thru G).

The severity of the risk of saccharin is in question. In the case of saccharin ingestion, only male rats (in laboratory tests) and male humans (in the one epidemiologic study that shows an association between saccharin use and bladder cancer) show a proclivity to the development of bladder cancer, although saccharin's cancer promotion effects appear equal among sexes.

The availability of a safe, economical, and esthetically acceptable non-caloric sweetener would obviate the need to select any of the options except A. When or if such an alternative will be available and approved is unknown. If implemented, Options B thru G could include a "sunset clause" stating that the policy option was operational for a fixed time before a saccharin ban to encourage the development of an alternative.

Options E thru G involve a policy other than that required by the Delaney Amendment. Scientists have varied attitudes concerning such a policy which examines only the risk of use of a food additive without consideration of compensating benefits of use or the hazards of non-use, but many agree that saccharin does not provide a good case study from which to develop an alternative policy that does consider compensating benefits because the potential health benefits of saccharin are yet to be proven.

APPENDIX H

WORK OF THE COMMITTEE

The Saccharin Study and Labeling Act (P.L. 95-203) requested that the National Academy of Sciences (NAS) examine the risks and benefits to health of saccharin use and consider the more general issues surrounding federal food safety policy. The NAS accepted the contract on January 20, 1978. The act specified that a report on saccharin would be submitted to FDA on November 1, 1978, and a report on general food safety policy would be submitted three months later. Because of the tight time schedule and the scope of the tasks, the Academy set up two panels—one (panel I) to address the saccharin issue and the second (panel II) to examine general food safety policy. A coordinating committee was formed to integrate the tasks of the two panels. Panel I submitted its report, Saccharin: Technical Assessment of Risks and Benefits to FDA on November 1, 1978.

This appendix describes the process by which the coordinating committee and panel II, with the advice and participation of some members of panel I, prepared the report on food safety policy in the United States. Table H-1 summarizes the chronology, from the acceptance of the contract to the report's submission to FDA in March, 1979. The committee and panel II consisted of experts of diverse backgrounds in order to consider as effectively as possible the multiple aspects of food safety policy. The committee and panel II each met separately twice during the initial phase of the study; the committee and panel II functioned as a single entity during the second half of the study.

Table H-1. Chronological sequence of events for food safety policy study.

								SUBPANEL MEETINGS						
Date	Public Law 95-203 passes	Contract Awarded	Coordinating Committee Meeting	Panel II Meeting	Panel I Meeting	Drafting Group Meeting	Public Hearing	Health Effects	Legal	Economic	Information and Education	Case Study Meeting	Saccharin Report Submitted	Food Safety Report Due
11/23/77	X													
1/20/78		X												
4/8			X											
4/29				X										
6/6-7				X										
6/20			X											
8/30						X								
9/7				X			X							
9/8			X	X										
10/5									X					
10/10								X						
10/13											X			
10/18										X				
10/21-22			X	X										
10/26									X					
11/1													X	
11/7-8												X		
11/27			X	X		X								
12/9-10						X								
1/22/79			X	X	X									
3/79														X

Note: Only discrete events are noted. Ongoing activities, such as preparation of papers or background material are omitted.

During the first half of the study, the panel and committee devoted effort to the collection of information relevant to food safety, at the same time providing opportunities for exchange among the several expert areas represented within the committee. The following individuals also met with the group to share viewpoints and expertise: Lennart Albanus, Swedish National Food Administration, Uppsala, Sweden; David Blumenthal, U.S. Senate Staff, Washington, D.C.; W. Gary Flamm, U.S. Food and Drug Administration, Washington, D.C.; Peter Barton Hutt, Covington & Burling Washington, D.C.; Michel Ibrahim, University of North Carolina, Chapel Hill, NC; Andrew D. Laumbach, U.S. Food and Drug Administration, Washington, D.C.; Stephen Lawton, U.S. House of Representatives Staff, Washington, D.C.; Mary Frances Lowe, U.S. Senate Staff, Washington, D.C.; Frank C. Lu, University of Miami, Miami, FL; Richard A. Merrill, University of Virginia Law School, Charlottesville, VA: Stuart Pape, U.S. Food and Drug Administration, Washington, D.C.; Richard Ronk, U.S. Food and Drug Administration, Washington, D.C.; I. Bernard Weinstein, Columbia University, New York, NY; Richard J. Wurtman, Massachusetts Institute of Technology, Boston, MA; and Richard Zeckhauser, Harvard University, Boston, MA.

Midway through the study, it became clear that smaller groups would be needed to consider special aspects; the work could not be done solely at monthly or bi-monthly meetings of the large group. At the same time a "drafting group" was formed to consider how best to present the findings and to coordinate and guide the preparation of the report. Arrangements also were made for subpanel meetings, by discipline, to consider in depth the specific problems within each discipline. Working papers by the subpanels and the drafting group were circulated to the full membership for reactions and several joint meetings of the committee and panel II were held for general discussion. The report therefore reflects individual and small group expertise as well as the views and recommendations of the panel and coordinating committee. The nature of the task and the limitations of the time necessarily left some issues short of full consensus as is indicated by some individual and group dissents that accompany this report.

Members of the drafting group were Frederick Robbins, Chairman of the Coordinating Committee; Emmanuel Farber, Chairman of panel I; Walter Rosenblith and Clifford Grobstein, Co-chairmen of panel II; and Don Price, a member of panel II whose special expertise in political science, administration, and government was invaluable. The drafting group communicated frequently by meetings and conference calls.

Four subgroups were established in the areas of health effects, law information and education, and economics. The meetings and attendees are listed below.

The Subpanel on Health Effects met on October 10th, in Washington, D.C., with Robert W. Miller as chairman. The following members attended: Charles C. Brown; T. Colin Campbell; Alfred E. Harper; George B. Hutchison and Beverly Winikoff.

The Subpanel on Law met twice. The first meeting was held in Washington, D. C. on October 5th, and the second in Boston, MA on October 26th. Don Price chaired both meetings. Members of this subpanel were: Stephen B. Breyer; Marshall S. Shapo; Thomas Ehrlich and Gordon Bloom. Consultants who participated in one or both meetings were: Peter Barton Hutt, Covington & Burling, Washington, D.C.; Richard Merrill, University of Virginia Law School, Charlottesville, VA; Charles Halpern, Institute for Public Representation, Washington, D.C.; and Thomas Troyer, Chaplan and Drysdale, Washington, D.C.

The Information and Education Subpanel discussed its area by conference call. Robert P. Abelson chaired the call. Other participants were: David L. Call, Jean L. Harris, Helen E. Nelson, and Beverly Winikoff.

Experts at an ad hoc meeting on economics, held in Boston, MA, on October 18th discussed the application of economic theory to problems of food safety. Robert Solow of Massachusetts Institute of Technology, Cambridge, MA chaired the meeting. Participants included: Kenneth Arrow, Rashi Fein, and Thomas Schelling, all from Harvard University, Cambridge, MA; and Jeffrey Harris, Peter Temin, and Paul Joskow, all from Massachusetts Institute of Technology, Cambridge, MA. Members of the committee and panels present were: Don Price, Sherwin Rosen, Sheldon W. Samuels, and Oliver E. Williamson. Richard Scheffler was the Staff Director of the Ad Hoc Committee on Economics of Food Safety

In fulfilling its mandate to consider how risks and benefits are related to regulation of particular substances in foods, the committee and panel used four case illustrations of current food safety problems. In order to insure as far as possible, scientific accuracy in presenting these illustrations and the issues they demonstrate, the individuals most closely associated with this part of the study held a two-day meeting in Chicago on November 7-8.

The meeting on Case Illustrations was chaired by Emmanuel Farber. Participants included: Fred P. Abramson, Charles C. Brown, T. Colin Campbell, Clifford Grobstein, Richard L. Hall; George B. Hutchison, Bert N. LaDu, Jr., Sherwin Rosen; and Marshall S. Shapo. A special guest was Richard Doherty, University of Rochester, Rochester, NY, who is an expert on methylmercury.

At the request of the committee and panel, various background papers were prepared by experts, consultants and staff researchers.

The list of papers prepared by experts follows:

Albanus, Lennart, The Swedish National Food Administration, Sweden. Food Safety Regulation in Sweden.

Dahle, Hans K, Veterinary College of Norway, Norway. Food Additives and Contaminants in Norway.

Lijinsky, William, Frederick Cancer Research Center, Frederick, MD. Evaluation of Risks Related to Nitrites, Nitrates and Nitrosamines.

Lu, Frank C., University of Miami, Miami, FL. International Activities in the Field of Food Additives.

Merrill, Richard A., University of Virginia Law School, Charlottesville, VA. (1) Regulation of Carcinogens in Food: Legislator's Guide to the Food Safety Provisions of the Federal Food Drug & Cosmetic Act. (2) FDA Use of The Delaney Clause.

The following consultants prepared background documents: Laura Green, Massachusetts Institute of Technology, Cambridge, MA; B. Lynn Allen-Hoffmann, Cornell University, Ithaca, NY; and Lawrence Miike, Private Consultant, Berkeley Springs, WV.

Staff researchers who provided background documents were: Donna Chew, Christiane E. Doerwaldt, Ellen Dorsch, Jeanne Holzgrefe, Michael Ronan, Florence Schwartz, and Jeffrey Trauberman.

In addition, members of the study staff contacted representatives from federal agencies to obtain information about regulating environmental hazards. Agencies contacted included the Food and Drug Administration, the Environmental Protection Agency, the Occupational Safety and Health Administration, the U.S. Department of Agriculture, and the Consumer Product Safety Commission.

To supplement information obtained from background papers and specialists, the committee and panels held a public meeting on September 7, 1978, at the National Academy of Sciences, Washington, D.C. Fifteen speakers presented varied viewpoints on issues of food safety regulation and these were considered as the report drafting proceeded. (Agenda follows).

The final report represents the views of a majority of the members of the panels and committee, although not all individuals concerned subscribe fully to all statements that appear in this report.

The committee and the National Academy of Sciences staff were helped immeasurably by the willingness of people, agencies and organizations listed here to share their information and insights. The committee and the NAS staff express deep appreciation to them. Particular thanks are due to the many staff members of the Food and Drug Administration who provided information and assistance throughout the performance of this task.

Agenda for the Open Meeting
Study on Saccharin and Food Safety Policy

September 7, 1978
AUDITORIUM

National Academy of Sciences
Assembly of Life Sciences/Institute of Medicine

TIME	SPEAKER'S NAME	AFFILIATION
9:00 am	Elena O. Nightingale, M.D., Ph.D.	Staff Director, Committee for a Study on Saccharin and Food Safety Policy Institute of Medicine
9:15 am	Frederick C. Robbins, M.D.	Dean, Case Western Reserve Medical School, Cleveland, Ohio and Chairman, Committee for a Study on Saccharin and Food Safety Policy
9:25 am	Walter A. Rosenblith, Ing. Rad.	Provost, Massachusetts Institute of Technology and Chairman, Panel II: Food Safety Regulation and Societal Impact
9:30 am	James Martin, Ph.D.	United States House of Representatives (North Carolina)
9:45 am	Jackson Browning	Corporate Director, Health Safety and Environmental Affairs Union Carbide Corporation
10:00 am	Robert Squire, DVM, Ph.D.	Johns Hopkins University (on behalf of the Food Safety Council)
10:15 am	Norman Jones, Jr., Ph.D.	Economic (on behalf of the Food Safety Council)
10:30 am	Betty Goldblatt, R.D., M.P.H.	Editor, Environmental Nutrition Newsletter
10:45 am	DISCUSSION	
11:00 am	COFFEE	

TIME	SPEAKER'S NAME	AFFILATION
11:15 am	Elizabeth Whelan, D.Sc., M.P.H.	Director, American Council on Science and Health
11:30 am	Anita Johnson, Esq.	Staff Attorney, Environmental Defense Fund
11:45 am	James Turner, Esq.	Law Firm of Swankin and Turner (on behalf of the Consumer liaison Panel, Food and Nutrition Board, National Academy of Sciences)
12:00 noon	James E. Mack	National Confectioners Association
12:15 pm	Robert Kellen	President, The Calorie Control Council
12:30 pm	Robert Choate	Council on Children, Merchandising & Media
12:45 pm	DISCUSSION	
1:00 pm	LUNCH	
2:00 pm	Jerome Heckman, Esq.	General Counsel, The Society of the Plastics Industry, Inc.
2:15 pm	Robert Harkins, Ph.D.	Vice President, Scientific Affairs Grocery Manufacturers of America
2:30 pm	Charles Blackmar, Esq.	Legal Counsel, Great Plains Legal Foundation (on behalf of the Howell County, Missouri Pork Producers Association)
2:45 pm	John M. Panza	Chairman, Committee on Public Affairs and Governmental Relations; Member, Board of Directors, American Diabetes Foundation
3:15 pm	DISCUSSION	
3:30 pm	COFFEE	

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APPENDIX I

GLOSSARY

Words are defined in the context of this report.

*Refers to legal terms. In this glossary, "the Act" refers to the Federal Food, Drug, and Cosmetic Act, as amended, 21 U.S.C. Sec. 321 et seq.

acrylonitrile. Vinyl cyanide; (CH_2CHCN). A clear, colorless, synthetic liquid used in manufacturing various products, including plastic bottles and cellophane. Has toxic properties and is apparently carcinogenic. Of concern because acrylonitrile molecules may migrate from plastic containers to food.

acrylonitrile copolymer. A copolymer is a high molecular weight material formed by combining simple unlike molecules in a repeating pattern. For acrylonitrile copolymers, one of the simple starting molecules is acrylonitrile (see above).

*action level. An interim limit set by FDA on the concentration of a substance permitted in food. The Act does not expressly authorize setting of action levels. They serve as warnings that FDA will consider "adulterated" any food not in conformity with the levels. Action levels do not have force of law. See: tolerance level.

additive. See: color additive, food additive, direct ingredient.

ADI (acceptable daily intake). The amount of a substance in food that if consumed each day has been judged to be without harmful effect. The ADI is usually expressed in terms of milligrams (mg) of the chemical per kilogram (kg) of the consumer's body weight.

*adulterated. Food is adulterated if it contains a poisonous or deleterious substance or a substance unfit for food. Adulterated food may not be used in commerce. (For complete definition, see the Act.)

aflatoxin. An organic compound produced by Aspergillus flavus molds that may contaminate some foods, particularly peanuts and corn. A potent liver carcinogen in many animals.

anthropometric. Related to human body measurements.

aryl hydrocarbon hydroxylase (AHH). See: mixed function oxidase.

ascorbic acid, ascorbate. Vitamin C, a reducing agent.

assay. (1) (verb) To measure or determine biological or chemical parameters. For example, the strength of an antibiotic preparation is assayed by determining how many bacteria it will kill under standard conditions; or one assays paint to see how much lead is in a particular volume of paint. (2) (noun) A measurement or method of measurement. For example, an assay shows how potent a drug is.

benefit. Positive effect, something that promotes well-being. Here limited to: Physiological health benefit - the effect of things that promote or protect physical health or prevent disease. Perceived or psychological benefit - the effect produced by things that are subjectively desired, that people want, or that people believe produce a desired effect. Economic benefit - reductions in production costs or reduction in the price of goods to consumers.

BHA (butylated hydroxyanisole). An antioxidant added to many foods, especially cooking oils, to prevent them from turning rancid.

botulism. A disease caused by an extremely potent toxin produced by the bacterium Clostridium botulinum. Improperly canned or improperly preserved foods may contain botulinum toxin, a result of bacterial growth. The disease is characterized by central nervous system and other symptoms and is often fatal.

calcium propionate. A substance that inhibits mold growth; used primarily in baked goods.

carcinogen. Any substance that produces cancer in animals or humans.

carcinogenesis. The production of cancer.

case-control study (retrospective). A study in which cases (i.e., diseased individuals) are selected and compared with controls (i.e., non-diseased individuals) to determine associations that might lead to identification of causes of disease.

casein. The principal protein of milk, curd and cheese.

cell culture. Cells grown in special glass or plastic dishes containing nutrients. Cell culture refers to the cells themselves or the process of growing the cells.

Chinese Restaurant Syndrome. A temporary set of symptoms associated with eating food containing monosodium glutamate (MSG). The syndrome is characterized by throbbing of the head, light-headedness, tightness of the jaw, neck, and shoulders.

choline. Generally considered one of the vitamins. Found in many animal tissues. Reacts in the body to form a compound (acetylcholine) that is necessary for transmitting nerve impulses.

chromosomes. Rod-shaped structures in the cell nucleus. The chromosomes consist of nucleic acids (DNA and RNA) and proteins. The DNA portion contains the genes (the hereditary information) of the cell.

clinical trial. Controlled study on humans designed to test or compare interventions.

cohort study. Epidemiologic studies of an outcome among members of a population. The group or groups of persons to be studied (cohort) are chosen prior to knowledge of the effect among them. Prospective cohort studies - the outcome has not yet occurred in the groups under study, but may appear during the course of the study. For example, one can study measles incidence among a cohort consisting of immunized and non-immunized children. Retrospective cohort studies - the outcome has already occurred. For example, one can do a retrospective cohort study among people exposed or not exposed to mustard gas in World War I to learn the effect of such exposure.

*color additive. The Act defines this term to include any synthetic or derived material that is capable of imparting color to a food, drug, or cosmetic, except for those substances used solely for a purpose other than coloring.

*Color Additive Amendments. This 1960 law amended the Act to establish provisions for the regulation of color additives.

*confounding factor. In epidemiologic studies, a factor that contributes to a disease incidence, and to which exposure frequently occurs under the same conditions as exposure to a substance whose effects are being studied. If confounding factors are present but ignored, an incorrect estimate of the effect of the substance under study may be made, because the effect of the confounding factor may incorrectly be attributed to the factor being studied.

contaminant. An impurity that enters food from the environment.

cultured cells. See: cell culture.

*Delaney clause. Provision of the Act, added in the Food Additives Amendment of 1958, that prohibits FDA from approving as a food additive any substance "found to induce cancer when ingested by man or animal" or in appropriate tests. Similar provisions apply to color additives and new animal drugs. Clause only applies to those substances that are legally defined as food additives (see Chapter 2 and Appendix B).

*direct food additive. A legal category that includes some but not all substances intentionally added to food during manufacture or processing. Excludes GRAS and prior sanctioned items, color additives, and various other substances.

direct ingredient. A non-legal category of substances that includes direct food additives, color additives, and intentionally added GRAS and prior sanctioned substances. Generally corresponds to popular use of term "additive."

DES (diethylstilbestrol; also spelled diethylstilbesterol). Steroid drug formerly given to some pregnant women to attempt to decrease the chance of miscarriage, but later associated with cancer of the vagina in daughters of these women. This drug is often fed to cattle to enhance their growth. DES residues have been found in beef liver.

desiccating. Drying. In this report, refers to removing moisture from food as a method of preserving the food.

dose. The concentration or amount of a substance to which an individual or group is exposed during a specified time period. For example, two standard 5-grain aspirins taken every day for one week would be a daily dose of 10 grains and a weekly dose of 70 grains; 14 aspirins all taken on one day during a 7-day test period would also be a weekly dose of 70 grains.

dose-response curves. Analysis of the quantitative relationship between exposure and effect, e.g., if the exposure (dose) is doubled, does the measured effect double?

electrophilic. Attracted to electrons, hence, tending to react chemically with substances containing accessible electrons. Many carcinogens are apparently electrophilic and react with DNA.

endemic goiter. Enlargement of the thyroid gland resulting from iodine deficiency and found in people living in areas where the iodine content of the usual diet is low. It can be prevented by supplementation of food items (such as salt) with iodine.

endosperm. A structure in seeds that contains reserve food materials for the plant embryo.

enteritis. Inflammation of the small intestine.

epidemiology. The study of the relationships of factors associated with the frequency and distribution of diseases in (human) populations.

epoxide. An organic molecule containing a three-membered ring consisting of one oxygen atom and two carbon atoms. This grouping is unstable and very reactive.

Escherichia coli (*E. coli*). A bacterium found in the intestines of humans and other animals. Laboratory strains of this bacterium are frequently used in genetic research.

etiology. The causes of a disease or abnormal condition.

eukaryotes. Organisms whose cells have a highly organized nucleus bounded by a nuclear membrane. Includes humans, insects, yeasts, trees, etc. Excludes viruses, bacteria, and certain algae.

expressed preference. Method of estimating benefits based on interviews, or on what people say they want. Distinguished from "revealed preference," a method of estimating benefits based on money spent on voluntary activities.

extrapolation. Extension of a graph or of data beyond the upper or lower limits of the actual measurements. The purpose is usually to estimate results under conditions where actual measurements cannot be made or were not made. In simple extrapolations, it is usually assumed that the proportionality between two factors will remain the same. For example, if measurements reveal that it takes a person 5 minutes to eat 1 apple and 10 minutes to eat 2 apples, it can be extrapolated (estimated) that it will take the person 2-1/2 minutes to eat half an apple and 20 minutes to eat 4 apples. Methods of extrapolation are rarely so straightforward, especially when used to estimate responses of animals to low doses of chemicals.

*Federal Food, Drug, and Cosmetic Act. Originally enacted in 1938 and frequently amended since then, this law provides the statutory authority for FDA regulation of foods, drugs, cosmetics, and medical devices.

fibroblasts. Connective tissue cells that form the fibrous tissues in the body. These cells grow readily in cell cultures and are frequently used for laboratory experiments.

*food additive. See: direct food additive and indirect food additive. Both categories of food additives are subject to the same provisions of the Act. GRAS and prior sanctioned substances are not considered food additives for purposes of the Act, and they are subject to different provisions.

*Food Additives Amendment. The 1958 amendment to the Act requires testing and approval of food additives before marketing (premarket approval). Includes the general safety clause, the Delaney clause, and the definition of "food additive" that excludes GRAS and prior sanctioned substances.

*Food and Drugs Act. The original 1906 law establishing federal regulation of drugs and prohibiting the adulteration of food; replaced in 1938 by the present Act that incorporated many of its provisions.

functional group. In chemistry, the group of atoms on a molecule that is responsible for the principal reactions or properties of the molecule.

gene. The unit of heredity. It is composed of deoxyribonucleates (DNA); it is self-replicating, is located in a definite position on a chromosome, and can specify a particular biological function.

*general safety clause of the Food Additives Amendment. The provision of the Act that prohibits FDA from approving a use of a food additive that is not proved safe.

*generally recognized as safe (GRAS). A substance is categorized as GRAS, and therefore not subject to the premarket testing and approval requirements of the Act applicable to food additives, if qualified experts generally agree that it has been shown to be safe for its intended use through adequate scientific procedures or, in the case of substances used before enactment of the Food Additive Amendments in 1958, through experience based on common use in food.

genome. The complete set of genes of the germ cells of an organism (e.g., an egg or sperm).

genotoxic. Harmful to the genes. Such harm could include changing the information the genes specify, or interfering with their ability to reproduce themselves accurately.

health benefit. See benefit—physiological health benefit.

heptachlor. A chlorine-containing insecticide toxic to humans.

hyperkinesis. Hyperactivity; the name given to the greater than usual amount of movement or activity seen in some children.

histidine. One of the essential amino acids (building blocks of proteins).

ileostomy. Surgical creation of an opening into the ileum (part of the small intestine), usually by establishing an opening of the ileum on the wall of the abdomen.

immunoblastic cell. A cell that can differentiate into a special type of cell capable of producing antibodies.

*indirect food additive. A substance whose use in food production may result, or may reasonably be expected to result, in its becoming a component of the food or affecting the characteristics of food. It is not added directly to the food. This category excludes substances that are GRAS or prior sanctioned, and direct food additives.

indirect ingredient. A non-legal term that includes indirect food additives, as noted above, and additional substances that are not indirect food additives for legal purposes under the Act. These additional substances include items that are: GRAS or prior sanctioned; new animal drugs; or pesticide residues.

initiation (of cancer). The first step or event in producing some cancers. Although not well understood, initiation is in some cases believed to be a mutational event, and is not thought to lead inevitably to cancer.

in vitro (in reference to biological experiments). Occurring outside a living organism, e.g., in a test tube.

in vivo (in reference to biological experiments). Occurring in a living organism.

latent period. The time elapsed between the occurrence or beginning of an exposure and the specified response. For cancer, refers to the time that may elapse between first exposure to a carcinogen and the eventual appearance of cancer.

lesion. Any discontinuity of tissue or loss of function of a part of a body due to trauma or disease.

logo. Graphic symbol conveying a message. Examples include: a skull and crossbones to indicate poison; a picture of a lighted cigarette with a bold line across it to convey "No Smoking"; and the distinctive brightly colored sign warning laboratory workers of the presence of radioactive material.

lymphoma. Abnormal growth or cancer of lymphoid tissue. Examples of lymphoid tissues are lymph nodes and tonsils. Example of a lymphoma is Hodgkin's disease.

lymphoreticular system. The system in the body that encompasses lymphoid tissue and macrophages, i.e., cells that engulf débris.

Mantel-Bryan mathematical extrapolation. One of several methods of estimating the effects of low doses of carcinogens, using data from animal experiments carried out with high doses. A slope of one probit (standard deviation) per 10-fold change in dose is commonly used.

Maumee process. One of the methods used in synthesizing saccharin. Starts with phthalic anhydride or anthranilic acid.

*maximum contaminant level. Under the Safe Drinking Water Act, the maximum level of a contaminant permitted in water delivered to any user of a public water system.

MCEL (minimum clinical effect level). The minimum exposure to a substance that causes an observable clinical effect. No measurable effect occurs at lower levels of the substance.

meiosis. A type of cell division that occurs during maturation of the sex cells. Meiosis reduces the number of chromosomes in sex cells to one half the number found in other body cells.

methemoglobinemia. The presence of excessive amounts of methemoglobin (an oxidized form of hemoglobin that does not combine with oxygen) in the red blood cells, resulting in an insufficient supply of oxygen carried to body cells.

3-methylcholanthrene. An organic chemical that is a potent carcinogen in laboratory animals.

microcalculi. Small stones found in the kidney, ureters, bladder, or other organs. Formed by deposit of mineral salts. Example is small kidney stones.

***misbranded.** Under the Act, food is misbranded if its label is false or misleading. Misbranded food may not be used in commerce.

mitosis. Nuclear division producing two daughter cells with exactly the same genetic material.

mixed function oxidase (MFO). Complex enzyme system that reacts with many chemicals that enter the body so that they can be more readily excreted. One measure of MFO activity is aryl hydrocarbon hydroxylase. Certain toxic substances, such as some pesticides, increase the activity of this enzyme system.

monosodium glutamate (MSG). A white crystalline chemical used to enhance the flavor of foods. Susceptible individuals may experience temporary symptoms after eating foods with sufficient amounts of MSG. See: Chinese Restaurant Syndrome.

mutagenic. Tending to cause structural changes in genes. Such changes are called mutations and can be inherited.

mycelia. The mass of threadlike structures (hyphae) that are a part of fungi or molds.

***natural constituent.** Innate component of a food. Example is vitamin C in oranges.

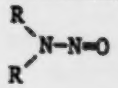
neoplasm. Any new abnormal growth; malignant neoplasm is another term for cancer.

Neurospora. A genus of fungi comprising the bread molds. Extensively used in genetic and enzyme research.

*new animal drug. Under the Act, a drug used for animals, or animal feed that contains drugs, but the term excludes animal feed (1) that contains a drug that is not generally recognized by experts as safe and effective or was not sanctioned before 1938 under the Food and Drugs Act, or (2) that contains a drug that is generally recognized as safe and effective but has not been used to a material extent. Antibiotic drugs are considered new animal drugs only under certain regulatory conditions.

nitrites. Inorganic compounds (salts of nitrous acid) added to smoked foods, meats, and poultry, that enhance flavor and color and prevent growth of botulism-causing organisms. Experiments show that nitrites can react with certain other substances to form nitrosamines, many of which are potent carcinogens. Recent animal studies suggest that nitrites themselves may be carcinogenic.

nitrosamines. A class of organic compounds with the following structure: Many nitrosamines are potent carcinogens.



nitroso compounds. Compounds that contain the group N=O. These compounds usually react readily with certain other compounds.

*notice-and-comment rulemaking. A type of administrative process used by an agency that involves announcement in the Federal Register of proposed agency actions and the opportunity for the public to comment on such proposals for agency consideration, without the opportunity for a formal hearing.

nutrient. 1) (noun). A food, substance, or chemical that is necessary for growth of cells or organisms. For humans, proteins, fats, and carbohydrates are considered macronutrients; vitamins and necessary minerals are considered micronutrients. 2) (adj). A nutrient medium is a mixture that supplies all of the chemicals needed for growth of a particular organism.

oncogenic. Giving rise to tumors or causing tumor formation. Can refer to certain viruses that cause tumors.

orthotoluenesulfonamide (OTS). The major impurity found in saccharin that is manufactured through the Remsen-Fahlberg process.

oxalic acid. An organic acid found in various plants. Used as a bleaching or cleaning agent.

parts per million (ppm). Microgram per gram. A method of expressing the relative amounts of two substances. For example, a gram of paint may contain 1 microgram of lead. The lead concentration in the paint would be 1 ppm.

periportal fibrosis of the liver. The formation of fibrous tissue around the arteries, veins, and bile ducts of the liver.

pharmacokinetics. The study of the action of a drug in the body over a period of time, including the processes of absorption, distribution, localization in tissues, metabolism, and excretion.

polybrominated biphenyl (PBB). A brominated hydrocarbon used as a flame retardant. Accidentally mixed with animal feed in Michigan a few years ago and caused symptoms in livestock and humans who ate the contaminated meat.

primates. Taxonomically, an order of mammals that includes humans, apes, monkeys, and lemurs.

*prior sanction. Approval granted to a substance, before enactment of the Food Additives Amendment in 1958, under the Federal Food, Drug, and Cosmetic Act, the Poultry Products Inspection Act, or the Meat Inspection Act.

probit model. One of several methods of using results of animal experiments that are carried out at high doses to estimate responses at low doses.

promoter (of cancer). A substance or exposure that encourages or enhances development of a tumor. Some promoters may not be able to cause a tumor to occur unless a preliminary step (initiation) has previously taken place in the cell(s) that will become a tumor.

prophylactic trial. Controlled study designed to evaluate the effectiveness of an intervention program to prevent disease.

raw agricultural commodity. An unprocessed food, such as a fruit or vegetable; any food in its raw or natural state.

relative or comparative benefit. The relationship of a benefit to other benefits (i.e., is A or B more valuable, useful, etc.).

Remsen-Fahlberg process. One of the methods used in synthesizing saccharin. The principal impurity present when this method is used is the starting material orthotoluenesulfonamide.

revealed preference. Method of estimating benefits based on the amount of money people spend on a voluntary activity.

Reye's syndrome. An acute and often fatal childhood disease marked by rapid development of brain swelling and fatty degeneration of some organs, including the liver, and by disturbed consciousness and seizures.

risk. (1) The probability of occurrence of an adverse effect of some specified nature. (2) Possibility of loss or injury.

Saccharin Study and Labeling Act. P.L. 95-203, enacted by the Congress in November 1977, authorizing this study, prohibiting a ban on saccharin pending results of the study, and establishing labeling requirements for saccharin products.

*safe. Standard of risk applicable to approval of food additives under the Act.

*standard. Something established as a way of judging adequacy, according to a specific criterion (such as risk or benefit) or a set of criteria (examples, "no probability of harm," "substantial economic benefit"); when the term applies to a set of regulated substances or products (such as carcinogens), it is also called a "generic," or general, standard, to distinguish it from individual substance-by-substance regulation. A standard can be very specific, such as 0.5 ppm, or very broad, such as "unsafe."

safrole. A natural carcinogen found in sassafras plants; formerly used as a flavoring.

The Salmonella/Ames test. A simple method of detecting agents that cause mutations in special strains of the bacterium _Salmonella typhimurium._ Also called _Salmonella_/microsome test, Ames test.

Salmonella typhimurium. Bacterium that infects warm-blooded animals and causes some food poisoning in humans. Special strains of _Salmonella_ are frequently used in genetic experiments.

secondary and tertiary amines. A class of organic compounds derived from ammonia.

short-term tests (for detecting potential mutagens and carcinogens). Any of the wide variety of tests designed to detect mutagens and carcinogens by determining whether a substance produces gene damage or cell transformation. These tests generally take a few days to a few weeks, although some may take as long as several months.

single event model (for carcinogenesis). Assumes that cancer begins in a single cell as the result of a random event, and that the probability of the occurrence of the event is proportional to exposure to conditions that may cause the event.

sodium nitrite. See: nitrites.

solanine alkaloids. Various bitter toxic substances found in parts of some plants of the nightshade family, including tomatoes and potatoes.

somatic mutation. A change in the genetic material of any body cell except sex cells (e.g., sperm or egg cells).

sorbic acid. A preservative added to many foods to prevent growth of molds and fungi.

sulfonamides. A group of compounds, some of which inhibit bacterial growth and are used to treat infections in humans.

synergism. Reinforcement that is more than simply additive. Used in the context that agents that would separately have an adverse effect, act synergistically to give a greater-than-additive adverse effect, e.g., breathing asbestos dust and smoking cigarettes act synergistically in increasing the risk of developing lung cancer far beyond the sum of the individual risks.

tannins. Various complex phenolic organic compounds found in plants. Used in tanning, drying, etc. Constituent of tea.

tardive dyskinesia. A disease that involves impairment of movement, resulting in fragmentary or incomplete movements and involuntary twitches of the facial muscles. Often induced by long-term use of neuroleptic drugs and may persist after withdrawal of such drugs.

teratogenesis. The production of defects in an embryo or fetus.

threshold. In this report, the minimum conditions of exposure necessary for a substance to affect health. Some effects may not have a threshold, that is, there are no known conditions of exposure where a substance that may cause an effect (e.g., cancer) is certain not to cause the effect.

*tolerance, or tolerance level. A formal regulatory limit on the amount of a substance permitted in food. The Act authorizes FDA to set tolerance levels for unavoidable added contaminants. Tolerance levels do have force of law.

*tort liability. A legal obligation, other than responsibility in criminal law, for injuring a person negligently or intentionally. Torts are civil wrongs, such as assualt, malpractice, or causing an automobile accident.

transformation (in reference to laboratory cultures of animal cells). A particular set of changes in cultured cells that causes the cells to resemble cancer cells in some ways. Most transformed cells will give rise to tumors when injected into an appropriate animal. Transformed cells will divide indefinitely in culture under proper conditions; non-transformed cells eventually stop dividing. Some viruses, some types of irradiation, and some chemical carcinogens may cause transformation of cultured cells under proper experimental conditions.

translocation. In genetics, the shifting of a segment of one chromosome onto a different chromosome.

*unavoidable added contaminant. A type of food contaminant that is not a natural constituent of the food and that cannot be avoided by good manufacturing practice. Example is aflatoxin.

urea. The chief nitrogen-containing constituent of urine, and the chief end-product of the metabolism of proteins.

xeroderma pigmentosum. A rare and frequently fatal disease accompanied by extreme sensitivity to sunlight. The disease is genetic, usually inherited as a recessive trait. Cells of people with this disease seem to have faulty DNA-repair processes, and these individuals have a tendency to develop carcinomas.

X-linked recessive mutations. Certain types of changes that occur in genes located on the X-chromosome. In females, the change will not be expressed unless the same change occurs on both X-chromosomes. In males, the change will always be expressed, since males have only one X-chromosome.